Cardiovascular Disease in the Elderly
FUNDAMENTAL AND CLINICAL CARDIOLOGY

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Cardiovascular Disease in the Elderly
Fourth Edition

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Series Introduction

Informa Healthcare has developed various series of beautifully produced books in different branches of medicine. These series have facilitated the integration of rapidly advancing information for both the clinical specialist and the researcher.

Wilbert S. Aronow, with coeditors Jerome L. Fleg and Michael W. Rich, has completely rewritten and updated the best-selling textbook *Cardiovascular Disease in the Elderly*. With the graying of our population, the fourth edition of this informative and comprehensive book becomes more important than ever before. The elderly require a special approach that includes a profound knowledge of geriatric epidemiology with regard to diagnosis, therapy, and preventive effort. I know that from my own clinical practice of cardiovascular medicine, as two of my patients celebrated their 100th birthdays this year.

The eight sections of this text are logically laid out, beginning with aging changes and focusing next on coronary disease, valvular heart disease, cardiomyopathy, and electrophysiology. The rest of this magnificent book covers cerebrovascular disease and miscellaneous but crucial topics such as quality of life in older patients with cardiovascular disease. This multiauthored text remains cohesive because the editors are also coauthors of multiple chapters in each section of the book.

My goal as editor-in-chief of the Fundamental and Clinical Cardiology Series is to assemble the talents of world-renowned authorities to discuss virtually every area of cardiovascular medicine. I feel we have achieved this objective with *Cardiovascular Disease in the Elderly, Fourth Edition*. Future contributions to this series will include books on molecular biology, interventional cardiology, and clinical management of such problems as coronary artery disease, venous thromboembolism, peripheral vascular disease, and cardiac arrhythmias.

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Editor-in-Chief
Fundamental and Clinical Cardiology Series
It should come as no surprise to any physician practicing medicine in an industrialized nation in the early years of the 21st century that the demography of the patient population has changed dramatically over the last three or four decades. Indeed, that there is a remarkable “graying” trend for both in- and outpatients in our society is an acknowledged fact immediately recognized by contemporary medical students, residents, subspecialty fellows, and practicing clinicians. In my own cardiology and internal medicine practice, more than half of the individuals that I treat fall into the geriatric category with their special needs, requirements, and problems. A simple clinical example demonstrates these issues exquisitely: An 85-year-old patient has symptomatic, critical aortic stenosis. Should this patient undergo life-prolonging aortic valve replacement surgery, and would such surgery represent “appropriate care” for this 85-year-old person? The answer to this question, of course, depends on many factors, not just the patient’s age and diagnosis. For example, what is the functional status, physically and mentally, of our 85-year-old patient? What comorbid conditions affect this individual? Finally, what does this patient want to do after the attendant risk and discomfort of the aortic valve operation have been described?

This clinical scenario is one that I face literally every week, and I suspect that most clinicians in our society do as well. I doubt that any cardiologist would disagree with a recommendation for “no surgery” if the described patient had severe advanced Alzheimer’s disease and was confined to a nursing home bed. On the other hand, if the patient were living independently and were vigorous and active, I suspect that just about every cardiologist would agree that this patient should undergo AVR if the patient agreed to the risk of mortal and morbid events associated with the operation.

The two extremes just described are rather straightforward; however, a large number of patients fall between the limits of these two examples. For this intermediate group of patients, the negotiation with the patients and their families can be complex, requiring special knowledge on the part of the practitioner. That is exactly the kind of information that is contained in this superb text, with its extensive compilation of geriatric cardiovascular topics. Building on several previous strong editions, the current book is authoritative, up to date, and well organized. Each chapter has been written by an acknowledged authority in the field of geriatric cardiology. This book should be required reading for every practicing cardiologist and every cardiology fellow currently in training.

Every modern clinician working today must face the reality of our changing population demographics: A tsunami of older patients has already been sighted, and it is
rapidly approaching our clinical coastline! These individuals will require special attention based on a thorough knowledge of the diagnostic and therapeutic strategies that differ in many ways from those of younger patients. The present text will enable physicians involved in the care of these elderly individuals to deliver quality, compassionate, and empathetic care to these patients, almost all of whom will have clinically important cardiovascular disease.

I recommend this important text to every physician who will have to deal with this burgeoning population of elderly individuals. As clinicians involved in the care of these geriatric patients, it is our professional responsibility to give them the very best health care possible. This book will help us do just that.

Joseph Alpert
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Preface to the Fourth Edition

In 2010, the first of the “baby boomers” will turn 65 years old. This event will herald an explosive growth in the older adult population in the United States, from just over 40 million in 2010 to approximately 72 million by 2030, an increase of 80%. Concomitantly, the proportion of the populace over age 65 will increase from about 1 in 8 to about 1 in 5. Accompanying this “graying of America” will be a dramatic rise in the number of older persons with clinically manifest—or at risk of developing—cardiovascular disorders, including hypertension, coronary artery disease, valvular heart disease, heart failure, and cardiac rhythm disturbances. Since persons over 65 already account for more than 80% of all deaths attributable to cardiovascular disease, it will become imperative in the years ahead for all clinicians involved in the care of older adults—not just primary care physicians, geriatricians, and cardiologists, but also surgeons, anesthesiologists, other medical subspecialists, and nurse practitioners—to have a basic understanding of the effects of aging on cardiovascular structure and function, as well as of the impact of aging and prevalent comorbid conditions on the clinical presentation, diagnosis, and response to therapy in older adults with cardiovascular disease.

As with prior editions, the primary objective of the present volume is to provide an up-to-date and in-depth, yet clinically relevant and “readable,” overview of the epidemiology, pathophysiology, evaluation, and treatment of cardiovascular disorders in older adults. All chapters have been thoroughly updated by recognized experts to incorporate the most recent developments in the field. To the extent possible, clinical recommendations are “evidence based,” but it is also acknowledged that existing data are often thin to nonexistent in the very elderly (persons 85 years of age or older), and especially in older adults with multiple coexisting conditions and/or frailty. Thus, careful consideration of each patient’s unique clinical and psychosocial circumstances, medical and nonmedical needs, and personal preferences is required in designing an individualized management plan. Indeed, it is perhaps in the compassionate management of these challenging patients where the “art of medicine” most clearly flourishes.

The first three editions of Cardiovascular Disease in the Elderly were published by Marcel Dekker in 1994, 1999, and 2004; i.e., at five-year intervals. With the fourth edition, Informa Healthcare has taken over as publisher, and publication has been accelerated by a year, primarily in response to the increasing volume of literature relevant to cardiovascular disease in older adults. It is noteworthy that the number of articles

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posted on Medline at the intersection of “cardiovascular disease” and “age greater than 65 years” increased from 1391 for the three-year period 1997–1999 to 1842 for the period 2000–2002, and to 2630 in the interval 2003–2005—a doubling in the number of citations over a nine-year period. In further recognition of the growing importance of the elderly population in cardiovascular medicine, an increasing number of clinical trials focusing on older adults have been undertaken, and practice guidelines are increasingly providing explicit commentary on the diagnosis and management of older adults.

With this edition, Dr. Michael W. Rich joins Drs. Wilbert S. Aronow and Jerome L. Fleg as coeditor. The general format of the text is similar to the previous edition. There are eight sections comprising 32 chapters, all written by recognized authorities in geriatric cardiology. The chapter topics remain the same as those in the third edition, with one exception. Information from the chapter “Pathophysiology of Coronary Artery Disease in the Elderly” has been incorporated into the other chapters on the diagnosis and treatment of this condition, while a new chapter, “Disability and Frailty in Older Patients with Cardiovascular Disease,” has been added.

We would like to thank all of the contributors for their outstanding work. We also wish to express our gratitude to Sandra Beberman at Informa Healthcare for her dedication and support in bringing this fourth edition to fruition. Finally, we want to thank you, the reader, for your commitment to providing the best possible care for your older patients with cardiovascular disease. We hope you will find this volume to be a valuable resource as you strive to help your older patients enjoy both longer and fuller lives. We welcome any comments you may have.

Wilbert S. Aronow
Jerome L. Fleg
Michael W. Rich
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Normal Aging of the Cardiovascular System

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INTRODUCTION

Since 1900, the average life expectancy for Americans has risen from 48 to 77.3 years. Over this period, the U.S. population expanded threefold, while the subset aged 65 and older increased 10-fold. The post–World War II baby boom will further expand this age group from the current 13% to 19.6% in 2030 (1). Furthermore, the fastest-growing age group, comprising those aged 85 years or older, has quadrupled since 1960 and will reach 19.5 million by 2030 (Fig. 1). Because both the prevalence and incidence of cardiovascular (CV) disease increase dramatically with age, this “graying” of the population has created a huge number of elderly patients requiring treatment. It must be emphasized, however, that aging per se is not necessarily accompanied by CV disease. This chapter will set the stage for those that follow by delineating the changes in the CV system that occur during the aging process in the absence of CV disease. This is a challenging task, given the many factors that blur their separation. Nevertheless, it is important to define normal CV structure and function in older adults to facilitate the accurate diagnosis of CV disease in this rapidly growing age group.

An additional theme of this chapter will be to indicate how aging changes in the CV system may themselves predispose to the development of CV disease. The enhanced CV risk associated with age indicates important interactions between mechanisms that underlie aging and those that underlie diseases. The nature of these interactions is complex and involves not only mechanisms of aging but also multiple defined and undefined (e.g., genetic) risk factors. The role of specific age-associated changes in CV structure and function has been, and largely continues to be, unrecognized by those who shape medical policy. Yet quantitative information on age-associated alterations in CV structure and function is essential to define and target the specific characteristics of CV aging that render it such a major risk factor.
Such information is also required to differentiate between the limitations of an elderly person that relate to disease and those that are within expected normal limits.

**METHODOLOGICAL ISSUES**

Numerous methodological issues must be addressed in attempting to define “normal” aging. Because the population sample from which norms are derived will strongly influence the results obtained, it should be representative of the general population. For example, neither a seniors running club nor nursing home residents would yield an appropriate estimate of maximal exercise capacity that could be applied to the majority of elders. Additionally, the degree of screening used to define a normal population can profoundly influence the results. In clinically healthy older adults, a resting electrocardiogram (ECG), echocardiogram, or exercise perfusion imaging study will often identify silent CV disease, especially coronary artery disease (CAD). If several such screening tests are used, only a small proportion of the older population may qualify as normal, limiting the applicability of findings to the majority of elderly individuals. Furthermore, the inclusion limits chosen for body fatness, blood pressure, smoking status, and other constitutional or lifestyle variables will significantly influence the normal values for measuring CV variables. For example, if a systolic pressure of ≥140 mmHg is considered hypertension, and if hypertension is considered a disease, then individuals with a systolic pressure between 140 and 160 mmHg, who a decade ago were thought to be normotensive, are now identified as having CV disease. Numerous studies have shown that individuals who manifest even modest elevations in systolic and pulse pressures are more likely to develop clinical disease or die from it.

Additional methodological factors can affect the definitions of normal aging. Cross-sectional studies, which study individuals across a wide age range at one time point, may underestimate the magnitude of age-associated changes because, in such studies, older normal persons represent “survival of the fittest.” True age-induced changes are better estimated by longitudinal studies, in which given individuals are examined serially over time. A reality of aging research, however, is that most data are derived from cross-sectional studies because they are easier to perform. Even longitudinal studies have their limitations—changes in methodology or measurement drift over time and development of disease in

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**Figure 1** Projected growth of the elderly population in the United States, stratified by age group.

*Source:* From Ref. 1
previously healthy persons. Finally, secular trends such as the downward drift in serum cholesterol or increasing obesity of Americans can alter age-related longitudinal changes.

In the current chapter, emphasis will be given to data obtained from community-dwelling samples screened for the absence of clinical, and in some cases subclinical, CV disease and major systemic disorders. A sizable portion of the data presented derives from the authors’ studies over the past three decades in community-based volunteers from the Baltimore Longitudinal Study of Aging (BLSA).

**UNSUCCESSFUL VASCULAR AGING AS THE “RISKY” COMPONENT OF AGING**

**Intimal Medial Thickening**

Aging changes in the arterial tree of individuals who are considered healthy may have relevance to the exponential age-associated increase in CV disease. Cross-sectional studies in humans have found that wall thickening and dilatation are prominent structural changes that occur within large elastic arteries during aging (2). Postmortem studies indicate that aortic wall thickening with aging consists mainly of intimal thickening, even in populations with a low incidence of atherosclerosis (3). Noninvasive measurements made within the context of several epidemiological studies indicate that the carotid wall intimal medial (IM) thickness increases nearly threefold between 20 and 90 years of age, which is also the case in BLSA individuals rigorously screened to exclude carotid or coronary arterial disease (Fig. 2, top panel).

Some investigators believe that the age-associated increase in IM thickness in humans represents an early stage of atherosclerosis (4). Indeed, excessive IM thickening at a given age predicts silent CAD (4). Since silent CAD often progresses to clinical CAD, it is not surprising that increased IM thickness (a vascular endpoint) predicts future clinical CV disease. A plethora of other epidemiological studies of individuals not initially screened to exclude the presence of occult CV disease have indicated that increased IM thickness is an independent predictor of future CV events. Note in Figure 2 (bottom panel) that the degree of risk varies with the degree of vascular thickening and that the risk gradation among quintiles of IM thickening is nonlinear, with the greatest risk occurring in the upper quintile (5). Thus, those older persons in the upper quintile of IM thickness may be considered to have aged “unsuccessfully” or to have “subclinical” vascular disease. The potency of IM thickness as a risk factor in older individuals equals or exceeds that of most other, more “traditional,” risk factors.

Age-dependent IM thickening has been noted in the absence of atherosclerosis, both in laboratory animals and in humans (3). Thus, the “subclinical disease” of excessive IM thickening is not necessarily “early” atherosclerosis. Rather, “subclinical disease” is strongly correlated with arterial aging. Interpreted in this way, the increase in IM thickness with aging is analogous to the intimal hyperplasia that develops in aortocoronary saphenous vein grafts, which is independent of atherosclerosis, but predisposes for its later development (6). Age-associated endothelial dysfunction, arterial stiffening, and arterial pulse pressure widening can also be interpreted in the same way. Combinations of these processes occurring to varying degrees determine the overall vascular aging profile of a given individual (i.e., the degree of “unsuccessful” vascular aging).

It is currently believed that additional risk factors (e.g., hypertension, smoking, dyslipidemia, diabetes, diet, or yet unidentified genetic factors) are required to interact with vascular aging (as described above) to activate a preexisting atherosclerotic plaque. According to this view, atherosclerosis that increases with aging is not a specific disease,
but an interaction between atherosclerotic plaque and intrinsic features related to vascular aging modulated by atherosclerotic risk factors. Evidence in support of this view comes from studies in which an atherogenic diet caused markedly more severe atherosclerotic lesions in older versus younger rabbits and nonhuman primates despite similar elevations of serum lipids (7,8). Hence, it is possible that atherosclerosis occurring at younger ages may be attributable not only to exaggerated traditional CV risk factors but also to accelerated aging of the vascular wall. Of course, the traditional risk factors may

Figure 2. (Top) The common carotid intimal-medial thickness in healthy BLSA volunteers as a function of age. (Bottom) Common carotid intimal-medial thickness predicts future cardiovascular events in the Cardiovascular Health Study. Abbreviation: BLSA, Baltimore Longitudinal Study of Aging. Source: (Top) From Ref. 4 and (Bottom) From Ref. 5.
themselves accelerate aging of the vascular wall. Studies in various populations with clinically defined vascular disease have demonstrated that pharmacological and lifestyle (diet, physical activity) interventions can retard the progression of IM thickening (9–14).

**Endothelial Dysfunction**

The endothelial monolayer that lines the luminal surface of the vascular tree plays a pivotal role in regulating multiple arterial properties, including vessel tone, permeability, response to inflammation, and angiogenesis. Several of these functions undergo important age-associated alterations. Endothelium-derived mediators such as nitric oxide (NO) and endothelin-1 are determinants of arterial tone and compliance, suggesting that endothelial cells may modulate arterial stiffness. Brachial arterial flow mediated dilation, mediated in large part by NO, declines with age in both sexes, even in the absence of other CV risk factors (15). A decline of ~75% in this flow-mediated vasodilation occurs in men between ages 40 and 70 years (Fig. 3). This decline begins approximately a decade later in women, perhaps because of the protective effect of estrogen, but is nearly 2.5 times as steep compared with men (15). The impairment of endothelial-mediated vasodilatation with aging in humans can be partially reversed by L-arginine administration, suggesting that NO production becomes reduced with aging (16). Plasma levels of asymmetric dimethyl arginine, which reduces nitric oxide synthase (NOS) activity, also increase with age in humans (16). The effect of age on endothelial function in central arteries, however,

![Flow Mediated Dilatation](image)

**Figure 3** Age-associated decline in endothelially mediated vasodilation in healthy volunteers. Note that the decline begins about a decade later in women than men, perhaps due to the protective effects of estrogen on endothelial function. *Source:* From Ref. 15.
has not been directly assessed in humans without clinical disease. In contrast to endothelium-mediated vasodilation, the vasodilator response to sublingual nitroglycerin is unrelated to age (15). Several CV risk factors and disorders are associated with endothelial dysfunction, including hypertension, hypercholesterolemia, insulin resistance, cigarette smoking, CAD, and heart failure. Furthermore, impaired endothelial vaso-reactivity, in both the coronary and peripheral arterial beds, is an independent predictor of future CV events (17,18). Hypertensive individuals exhibit endothelial dysfunction (19,20), and the mechanisms underlying their endothelial dysfunction are similar to those that occur with normotensive aging, albeit they appear at an earlier age (20). The normotensive offspring of hypertensives also exhibit endothelial dysfunction (21), suggesting that endothelial dysfunction may precede the development of clinical hypertension. Age-associated endothelial dysfunction, arterial stiffening, and IM thickening are risk factors for arterial diseases, even after accounting for other risk factors, such as arterial pressure, plasma lipids, smoking, etc. The interaction between arterial wall stiffening and CV diseases may set in motion a vicious cycle. In this cycle, alterations in the mechanical properties of the vessel wall contribute to endothelial cell dysfunction and, ultimately, to arterial stiffening.

### Arterial Stiffness and Compliance

The increase in arterial wall thickening and reduction in endothelial function with advancing age are accompanied by an increase in arterial stiffening and a reduction in compliance. Age-associated structural changes in the arterial media that increase vascular stiffness include increased collagen content, covalent cross-linking of the collagen, reduced elastin content, elastin fracture, and calcification (22,23). Strictly speaking, stiffness and its inverse, distensibility, depend on intrinsic structural properties of the blood vessel wall that relate pressure change with a corresponding change in volume.

### Pulse Wave Velocity

Each systolic contraction of the ventricle generates a pressure wave that propagates centrifugally down the arterial tree, slightly preceding the luminal flow wave generated during systole. The propagation velocity of this wave is proportional to the stiffness of the arterial wall. The velocity of the pulse wave in vivo is determined not only by the intrinsic stress/strain relationship (stiffness) of the vascular wall, but also by the smooth muscle tone, which is reflected by the mean arterial pressure.

Noninvasive measures of the velocity of this pulse wave allow for large-scale epidemiological studies to examine its determinants and prognostic importance. In both rigorously screened normal subjects (24) and populations with varying prevalence of CV disease (25–27), a significant age-associated increase in pulse wave velocity (PWV) has been observed in men and women (Fig. 4A). In contrast to central arteries, the stiffness of muscular arteries does not increase with advancing age (28). Thus, the manifestations of arterial aging may vary among the different vascular beds, reflecting differences in the structural compositions of the arteries and, possibly, differences in the age-associated signaling cascades that modulate the arterial properties, or differences in the response to these signals across the arterial tree.

Increased PWV has traditionally been linked to structural alterations in the vascular media, such as those observed with aging. Prominent age-associated increases in PWV have been demonstrated in populations with little or no atherosclerosis, again
indicating that these vascular parameters are not necessarily indicative of atherosclerosis (29). However, more recent data emerging from epidemiological studies indicate that increased large vessel stiffening also occurs in the context of atherosclerosis (30,31), metabolic syndrome (32), and diabetes (33,34). The link may be that stiffness is governed not only by the structural changes within the matrix, as noted above, but also by endothelial regulation of vascular smooth muscle tone and other aspects of vascular wall structure/function. Thus, there is evidence of a vicious cycle: altered mechanical properties of the vessel wall facilitate the development of atherosclerosis, which in turn increases arterial stiffness via endothelial cell dysfunction and other mechanisms.
Reflected Pulse Waves

In addition to the forward pulse wave, each cardiac cycle generates a reflected wave, originating at areas of arterial impedance mismatch, which travels back up the arterial tree toward the central aorta, altering the arterial pressure waveform. This reflected wave can be noninvasively assessed from recordings of the carotid (25) or radial (35) arterial pulse waveforms by arterial applanation tonometry and high-fidelity micromanometer probes. Dividing the late systolic augmentation of the arterial pulse wave by the distance from the peak to the trough of the arterial waveform (corresponding to the pulse pressure) yields the augmentation index (24). The augmentation index, like the pulse wave velocity, increases with age (Fig. 4B) (24,25).

The velocity of the reflected flow wave is proportional to the stiffness of the arterial wall. Thus, in young individuals whose vascular wall is compliant, the reflected wave does not reach the large elastic arteries until diastole. With advancing age and increasing arterial stiffening, the velocity of the reflected wave increases, and the wave reaches the central circulation earlier in the cardiac cycle, during the systolic phase. The pressure pulse augmentation provided by the early return of the reflected wave is an added load against which the aged ventricle must contract. Furthermore, the diastolic augmentation seen in compliant vessels, caused by the late return of the reflected waves, is lost in the elderly, decreasing diastolic blood pressure; this decrease in diastolic pressure has the potential to reduce coronary blood flow because most coronary flow occurs during diastole.

Multiple studies (27,36–43) indicate that increased vascular stiffness, over and above blood pressure, is an independent predictor of hypertension, atherosclerosis, CV events, and mortality. In fact, Liao et al. (38) have demonstrated that increased vascular stiffness precedes the development of hypertension. Thus, while a “secondary” increase in large artery stiffness is attributable to an increase in mean arterial pressure that occurs in hypertension, evidence now exists that a “primary” increase in large artery stiffness that accompanies aging gives rise to an elevation of arterial pressure. Normotensive individuals who fall within the upper quartile for measures of arterial stiffness are more likely to subsequently develop hypertension. Observations such as these reinforce the concept that hypertension, at least in part, is a disease of the arterial wall. The mechanisms of age-associated changes in vascular structure and function and the putative relationship of these changes to development of CV disease are depicted in Table 1.

Systolic, Diastolic, and Pulse Pressure

Arterial pressure is determined by the interplay of peripheral vascular resistance and arterial stiffness; the former raises both systolic and diastolic pressure to a similar degree, whereas the latter raises systolic but lowers diastolic pressure. A rise in average systolic blood pressure across adult age has been well documented (Fig. 5) (43,44). In contrast, average diastolic pressure (Fig. 5) was found to rise until about 50 years of age, level off from age 50 to 60, and decline thereafter (43,44). Thus, pulse pressure (systolic minus diastolic), a useful hemodynamic indicator of conduit artery vascular stiffness, increases with age. These age-dependent changes in systolic, diastolic, and pulse pressures are consistent with the notion that in younger people blood pressure is determined largely by peripheral vascular resistance, whereas in older individuals it is determined to a greater extent by central conduit vessel stiffness.

Because of the decline in diastolic pressure in older men and women in whom systolic pressure is increased, isolated systolic hypertension emerges as the most common
form of hypertension in individuals over the age of 50 (43). Isolated systolic hypertension, even when mild in severity, is associated with an appreciable increase in CV disease risk (45,46). On the basis of long-term follow-up of middle-aged and older subjects, however, Framingham researchers have found pulse pressure to be a better predictor of coronary disease risk than systolic or diastolic blood pressures (47). A subsequent Framingham investigation found that pulse pressure was especially informative of coronary risk because of the “J”- or “U”-shaped association between diastolic pressure and coronary risk. Thus, consideration of the systolic and diastolic pressures jointly, as reflected in pulse pressure, is preferable to consideration of either value alone.
INTERVENTIONS TO RETARD OR PREVENT ACCELERATED ARTERIAL AGING

Although the deleterious effects of aging on arterial structure and function may appear inevitable from the discussion above, increasing evidence is accruing that lifestyle modifications, including aerobic exercise and dietary modifications, including reduction in sodium intake, caloric restriction, or weight loss, can prevent or retard the progression of IM thickening (49–51) or arterial stiffening (52,53) and improve endothelial function ((54–57). Perhaps, the most promising of these modifications is caloric restriction, which prolongs maximal lifespan in laboratory animals when begun in youth or middle age. Limited studies in individuals have demonstrated decreases in CV risk factors and inflammatory markers with caloric restriction (51,58). In a recent study, 25 individuals aged 53±12 years who had practiced voluntary caloric restriction of ~30% for an average of 6.5 years showed markedly lower blood pressure and inflammatory markers compared with controls matched for age and gender (58). In addition, the calorie restricted group demonstrated higher transmitral early diastolic flow measures, similar to those of younger adults (58). Whether such beneficial effects can be derived by initiating caloric restriction at older ages is unclear.

Pharmacological interventions can also favorably modulate the elements of arterial aging. In animal models, chronic angiotensin converting enzyme inhibition or angiotensin receptor blockade, begun at an early age, markedly delays the progression of age-associated arterial remodeling, e.g., the IM thickening and rupture of internal elastic lamina (59,60), attenuates mitochondrial dysfunction, reduces reactive oxygen species,
enhances NO bioavailability, reduces fibrosis, retards vascular and cardiac aging, and prolongs life (61–67). It is thus far unproven if such treatment can prevent or retard unsuccessful aging of the vasculature in animals or humans of younger to middle age who exhibit excessive subclinical evidence of accelerated arterial aging. Recent studies have shown that breaking nonenzymatic collagen cross-links with a novel thiazolium agent reduces arterial stiffness, both in nonhuman primates (68) and in humans (69).

CARDIAC STRUCTURE AND RESTING FUNCTION

Before the advent of echocardiography, autopsy was essentially the only method for obtaining reliable measurements of cardiac structure in normal persons. Such studies were obviously flawed by their inherent selection bias. A large autopsy series by Linsbach et al. (70) in 7112 patients demonstrated an increase in cardiac mass of 1 to 1.5 g/yr between the ages of 30 and 90 years. Because the study included individuals with CV disease, the age-associated increase in heart weight may derive, at least in part, from the development of cardiac pathology. An autopsy study of 765 normal hearts from persons 20 to 99 years old who were free from both hypertension and CAD showed that heart weight indexed to body surface area was not age related in men but increased with age in women, primarily between the fourth and seventh decades (71). In hospitalized patients without evidence of CV disease, Olivetti et al. (72) observed an age-associated reduction of left ventricular (LV) mass mediated by a decrease in estimated myocyte number, although myocyte enlargement occurred with age. These investigators subsequently found a higher prevalence of apoptotic myocytes in older male than in female hearts, which paralleled a decline of LV mass with age in men but not in women (73).

Beginning in the 1970s, the widespread application of echocardiography finally allowed accurate noninvasive assessment of age changes in cardiac structure and function. In healthy normotensive BLSA men, Gerstenblith et al. (74) observed a 25% increase in echocardiographic LV posterior wall thickness between the third and eighth decades, a finding replicated by others (75,76). Because LV diastolic cavity size was not significantly age related in the BLSA (64), calculated LV mass also increased substantially with age. Thus, an apparent discrepancy existed between the unchanged or decreased LV mass with age seen at autopsy and the increase in LV wall thickness and calculated LV mass observed by echocardiography. A recent study in BLSA volunteers using cardiac magnetic resonance imaging (MRI) to estimate LV mass helps to resolve these divergent findings (77). Unlike standard echocardiography, which provides one- and two-dimensional measurements, MRI assesses LV size in three dimensions. In 136 men and 200 women without CV disease, MRI-derived LV wall thickness increased with age (Fig. 6, upper panels), and short-axis diastolic dimension was not age related, similar to earlier echocardiographic findings. In contrast, LV length declined with age in both sexes (i.e., the LV became more spherical) (Fig. 6, middle panels) (77). Thus, MRI-derived LV mass was unrelated to age in women and demonstrated an age-associated decline in men (because of their lesser age-related increase in wall thickness), similar to recent autopsy findings (Fig. 6, lower panels) (73). Three-dimensional echocardiography has confirmed this preservation of LV mass across age in women and a reduction of LV mass in older men (78). With advancing age, therefore, the normal LV becomes thicker and more spherical.

Although the mechanisms for the age-associated remodeling of the LV and increase in myocyte size are not clear, it is attractive to suggest that they are adaptive to the arterial
Fleg and Lakatta

(A) Women

LV Wall Thickness / Ht (cm/m) vs Age

- P < 0.001
- r = 0.41

Men

LV Wall Thickness / Ht (cm/m) vs Age

- P = 0.07
- r = 0.24

(B) Women

LV Length / Ht (cm/cm) vs Age

- P < 0.01
- r = -0.21

Men

LV Length / Ht (cm/cm) vs Age

- P < 0.0001
- r = -0.38

(C) Women

LVMI / BSA (g/m²) vs Age

- p = NS
- r = 0.04

Men

LVMI / BSA (g/m²) vs Age

- P < 0.03
- r = -0.26
changes that accompany aging. Putative stimuli for cardiac cell enlargement with age are an increase in vascular load due to arterial stiffening and a stretching of cells due to dropout of neighboring apoptotic myocytes (79,80). Phenotypically, the age-associated increase in LV thickness resembles the LV hypertrophy that develops from hypertension. This finding, coupled with the increase in systolic blood pressure that occurs over time even in healthy individuals, has led to consideration of aging as a muted form of hypertension. In older rodent hearts, which demonstrate a similar increase in LV mass and myocyte size as observed in humans, a stretching of cardiac myocytes and fibroblasts releases growth factors such as angiotension II, a known stimulus for apoptosis (81). In addition, enhanced secretion of atrial natriuretic (82) and opioid (83) peptides is observed.

Echocardiographic aortic root diameter dilates modestly with age, approximating 6% in BLSA men between the fourth and eighth decades (74). Similarly, the aortic knob diameter increased from 3.4 to 3.8 cm on serial chest x-rays over 17 years (84). Such aortic root dilation provides an additional stimulus for LV hypertrophy because the larger volume of blood in the proximal aorta represents a greater inertial load that must be overcome before LV ejection can begin.

As previously noted, the resting supine LV short-axis diastolic dimension is not significantly related to age; the resting LV systolic dimension is, similarly, unrelated to age. Thus, echocardiographic LV shortening fraction (64) and radionuclide LV ejection fraction (85,86), the two most common measures of global LV systolic performance, are unaffected by age in healthy normotensive persons. Because LV stroke volume (SV) is the difference of LV end-diastolic (EDV) and end-systolic volumes (ESV), the supine LV stroke volume is also unrelated to age (74). Prolonged contractile activation of the thickened LV wall (87) maintains a normal ejection time in the presence of the late systolic augmentation of aortic impedance, preserving systolic cardiac pump function at rest. However, a “downside” of prolonged contractile activation is that at the time of the mitral valve opening, myocardial relaxation is less complete in older than in younger individuals, contributing to a reduced early LV filling rate.

In contrast, therefore, to the preservation of resting LV systolic performance across the adult age span, LV diastolic performance is profoundly altered by aging. Reduced mitral valve E–F closure slope on M-mode echocardiography first documented these age changes in diastolic performance (74,75). Pulsed Doppler (88,89) and radionuclide (90) techniques confirmed that the transmirtal early diastolic peak-filling rate declined by ~50% between ages 20 and 80 years (Fig. 7). Conversely, peak A-wave velocity, which represents late LV filling facilitated by atrial contraction, increases with age. This greater atrial contribution to LV filling is accomplished via a modest age-associated increase in left atrial size demonstrable on echocardiography. Tissue Doppler and color M-mode techniques, both less influenced by preload and afterload than pulsed Doppler, have confirmed the age-associated reduction in early diastolic filling rate and increased late filling (91,92). Because the resting LV end-diastolic volume is preserved across adult age

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**Figure 6** Effect of age on LV geometry and mass, derived from three-dimensional cardiac magnetic resonance imaging in normotensive BLSA volunteers. (A) LV wall thickness increases with age in both sexes, though more steeply in women. (B) The LV long axis dimension declines with age in both sexes, but more steeply in men, whereas minor axis dimension (not shown) is unrelated to age. (C) Calculated LV mass is not age-related in women but declines with age in men. *Abbreviations: LV, left ventricular; BLSA, Baltimore Longitudinal Study of Aging. Source: Adapted from Ref. 77.*
in BLSA volunteers, the augmented atrial contribution to LV filling in older adults can be considered a successful adaptation to the reduced early diastolic filling rate in the thicker, and presumably stiffer, senescent LV. Thus, the relative importance of early and late diastolic LV filling is reversed with advanced age.

Impairment of early LV filling with age may derive in part from reduced LV diastolic compliance due to the increase in LV wall thickness with age. Although an age-associated reduction in ventricular compliance remains unproven in humans, animal studies in both intact hearts and isolated cardiac muscle have detected prolonged isovolumic relaxation and increased myocardial diastolic stiffness. The slower isovolumic relaxation observed in cardiac muscle from older animals (93) may be secondary to diminished rate of Ca\(^{2+}\) accumulation by the sarcoplasmic reticulum (94). A conceptual framework for the cardiac adaptations to age-associated arterial stiffening is shown in Figure 8.

Whereas the diminished early diastolic filling rate with age may not compromise resting end-diastolic volume or stroke volume, an underlying reduction of LV compliance might cause a greater rise in LV diastolic pressure in older persons, especially during stress-induced tachycardia, thus causing a lower threshold for dyspnea than in the young. It might also be anticipated that the loss of atrial contribution to LV filling that occurs during atrial fibrillation would elicit a greater deterioration of diastolic performance in older than in younger individuals. Indeed, it is attractive to speculate that the frequent occurrence of heart failure in the elderly despite preserved LV systolic function derives, at least in part, from the age-associated impairment of early diastolic filling (Table 1).

**CV Physical Findings in Older Adults**

Several age-associated alterations in CV structure and function may manifest themselves during the CV examination. Because of the stiffening of the large arteries, systolic blood
pressure is often elevated with a normal or low diastolic blood pressure. Therefore, the carotid artery upstroke is usually brisk in the elderly and may mask significant aortic valve stenosis. The apical cardiac impulse may be difficult to palpate secondary to senile emphysema and chest wall deformities. Respiratory splitting of the second heart sound is audible in only *30–40% of individuals older than 60 years, presumably because of reduced compliance of the pulmonary vasculature. In contrast, an S4 gallop is commonly heard in older but not younger persons because of the age-associated increase in late diastolic filling mediated by vigorous atrial contraction into a thicker-walled, less compliant LV. A soft basal ejection murmur occurs in 30–60% of the elderly. This murmur is thought to arise from a dilated, tortuous aorta or from sclerosis of the aortic valve.

**CV RESPONSE TO STRESS**

The CV response to stress (e.g., to increases in arterial pressure, to postural maneuvers, or to physical exercise) in older individuals is of considerable interest in clinical medicine. First, physicians are often called upon to provide advice and information concerning the CV potential of the elderly (e.g., the effect or importance of conditioning status on the maintenance of function). Second, the CV response to stress is important in assessing the ability of older individuals to respond to disease states. Third, the CV response to stress has considerable value in the diagnosis and management of patients with CV disease. Despite the high prevalence of CV disease among older Americans, it is of substantial importance to understand the exercise capabilities of disease-free CV elders. Exercise testing is a diagnostic tool that is frequently utilized to detect and quantify the severity of CV disease. It is very clear that the value of such diagnostic tests and the validity of their interpretation depend on precise information regarding the normal limits of such stress-testing procedures relative to age.
Orthostatic Stress

Perturbations from the supine, basal state activate CV reflex mechanisms and mediate the utilization of CV reserve function. The result of these reflex mechanisms is enhanced blood flow to, and preservation of arterial pressure within, selected body organs. In response to a change from supine to upright posture, an increase in systemic vascular resistance maintains the mean arterial pressure. A change in blood flow from the heart depends on the product of changes in heart rate and stroke volume index (SVI), the latter being determined by the changes in end-diastolic volume index (EDVI) and end-systolic volume index (ESVI). Changes in EDVI are determined, in part, by changes in venous return, which depends on the ability of the blood to flow through the vascular system, and to changes in ESVI.

In healthy, community-dwelling elders, arterial pressure changes little with the assumption of upright posture, and postural hypotension or acute orthostatic intolerance (i.e., dizziness or fainting when assuming an upright from a supine position or during a passive tilt) is uncommon. Orthostatic hypotension (OH), defined by a decline of systolic blood pressure by ≥20 mmHg or diastolic blood pressure by ≥10 mmHg, occurred in 16% of volunteers aged 65 years and older from the Cardiovascular Health Study (95) and in 7% of men aged 71 to 93 years from the Honolulu Heart Program (96); in both of these older cohorts the prevalence of OH increased with age. In the former study, OH was associated with higher supine blood pressure, greater LV wall thickness, and smaller LV cavity size (97). In the latter study, OH was an independent predictor for mortality (relative risk [RR] = 1.64), and there was a linear relationship between the magnitude of orthostatic decline in systolic blood pressure and 4-year mortality rate (96). In contrast to healthy, community-dwelling older volunteers, OH and orthostatic intolerance are common in debilitated institutionalized elders with chronic illnesses. Within such populations, the likelihood for OH is increased among individuals who exhibit very low LV filling rates and small EDVI and SVI in the supine position (98). In such individuals, however, the effects of advanced age cannot be dissociated from those of profound deconditioning and multiple diseases and medications.

With advancing age, the acute heart rate increase to orthostatic stress decreases in magnitude and takes longer to achieve. The baroreceptor sensitivity (i.e., the slope of the relationship of the change in heart rate versus the change in arterial pressure) is negatively correlated with age and resting arterial pressure (99). The low-pressure baroreceptor, or cardiopulmonary reflex, also decreases with age in normotensives, but not in hypertensives.

Despite the lesser heart rate increase during orthostatic stress in older than in younger BLSA volunteers, the SVI reduction tends to be less in the older group; thus, the postural change in cardiac output does not vary significantly with age, because a lesser reduction in SVI balances the lesser increase in heart rate in older individuals (100). Similarly, studies have found cardiac output to be reduced with age in the supine position because of a reduced SVI in older versus younger men; this age effect was abolished in the sitting position because of lesser reduction in SVI in the older men on sitting. Responses to gradual tilt or to graded lower body negative pressure in older individuals are similar to responses to change in body position: SVI and cardiac output decrease less in older adults, offsetting their blunted heart rate increase (101). A lesser reduction in SVI in older versus younger individuals following a postural stress implies either a smaller reduction in EDVI or a greater reduction in ESVI in older individuals. Reduced venous compliance in older versus younger individuals, advanced as a mechanism to account for a lesser peripheral fluid shift during orthostatic maneuvers, could preserve cardiac filling
volume and maintain SV in the upright position in healthy elderly individuals (102). A reduction in the venodilatory response to β-adrenergic stimulation with preservation of the α-adrenergic vasoconstrictor response may contribute to a reduced venous compliance with aging.

**Pressor Stress**

Acute increases in blood pressure represent another common CV stress. Sustained, isometric handgrip increases both arterial pressure and heart rate. The response varies in magnitude in proportion to the relative level and duration of effort. After sustained submaximal or maximal handgrip, heart rate was observed to increase more in younger than in older healthy individuals, whereas blood pressure increased more in older persons (103,104). In BLSA volunteers, 3 minutes of submaximal sustained handgrip elicited mild increases in echocardiographic LV diastolic and systolic dimensions and atrial filling fraction; these increases correlated positively with age (104). Thus, pressor stress accentuated the age-associated dependence on late diastolic filling.

Application of a pressor stress has also been used to assess the intrinsic myocardial reserve capacity. In healthy BLSA individuals, a 30 mmHg increase in systolic blood pressure induced by phenylephrine infusion in the presence of β-adrenergic blockade induced significant echocardiographic LV dilatation at end diastole in healthy older (60–68 years), but not in younger (18–34 years), men: the cardiac dilatation occurred in older men despite a smaller reduction in heart rate (105), analogous to the handgrip response. Thus, an apparent age-associated decrease in intrinsic myocardial contractile reserve occurs in response to an acute increase in afterload; the senescent heart dilates to preserve SVI via the Frank-Starling mechanism.

**Aerobic Exercise Capacity and Aging**

The ability to perform oxygen-utilizing (i.e., aerobic) activities is a fundamental requirement of independent living and is probably the best-studied CV stressor. The accepted standard for aerobic fitness is maximum oxygen consumption rate (VO$_2$max), the product of cardiac output (the central component) and arteriovenous oxygen difference (the peripheral component). In healthy adults, VO$_2$max is up to 15 times greater than VO$_2$ at rest. This is accomplished by a four- to fivefold increase in cardiac output and up to a threefold widening of the arteriovenous oxygen difference; the latter is due to both a dramatic increase in the relative proportion of cardiac output delivered to working muscles and an increased oxygen extraction by these muscles. Because the total body VO$_2$max is strongly influenced by muscle mass, VO$_2$max is typically compared across individuals by normalizing for body weight.

Numerous studies have documented that treadmill VO$_2$max, adjusted for body weight, declines with age. In cross-sectional studies, the decline typically approximates 50% across the adult age span. However, the extent of the VO$_2$max decline with aging varies among studies, depending on age ranges, differences in body weight and composition, and differences in habitual physical activity among the individuals studied. Longitudinal studies generally report a more pronounced age-associated decline in VO$_2$max than do cross-sectional studies. In BLSA volunteers rigorously prescreened to exclude CV or lung disease, VO$_2$max declines by ~50% between the third and ninth decades by cross-sectional analysis (Fig. 9) (106,107).

Cross-sectional studies, such as those in Figure 9, are usually interpreted to indicate that VO$_2$max declines linearly with age. A recent analysis in this same population, however, demonstrated that the longitudinal decline in aerobic capacity is not constant
across adulthood as assumed by cross-sectional studies, but accelerates markedly with
successive age decades, especially in men, regardless of physical activity levels (Fig. 10)
(108). When the components of VO2max were examined, the longitudinal decline in
oxygen pulse (VO2 per heart beat) mirrored that of VO2max, whereas maximal heart rate
decreased only 4–6% per decade regardless of starting age (Fig. 10). Although age-
associated loss of muscle mass and increase in body fat also contribute to the reduction in
VO2max with aging, the pattern of accelerated VO2max decline with age persists even
after normalizing it for fat-free mass rather than body weight (108). Despite the similar
rates of decline in VO2max with age regardless of physical activity level, it should be
emphasized that at any age the more active quartiles maintain a higher VO2 max than their
sedentary peers.

The accelerated decline of aerobic capacity has important implications regarding
functional independence and quality of life. One should bear in mind that the data in
healthy BLSA volunteers represent a “best case scenario.” The superimposition of CV or

Figure 9 Cross-sectional declines in peak VO2 per kg body weight in healthy BLSA men and
pulmonary disease as well as the deconditioning commonly seen in the elderly because of their sedentary lifestyle accentuates this decline in VO2max. Because activities of daily living typically require a fixed aerobic expenditure, they require a significantly larger percent of VO2max in an older than a younger person. Once the energy required of an activity approaches or exceeds the aerobic capacity of an elderly individual, he or she will likely be unable to perform it. Thus, it is not surprising that a low aerobic capacity comprises one of the five components of the “frailty phenotype” (109).

Another potential contributor to exercise intolerance with aging is a greater metabolic debt incurred during exercise that persists during recovery. For several minutes after a bout of aerobic exercise, the body continues to consume oxygen at a higher rate than at rest. This “oxygen debt” incurred during recovery can comprise 14–20% of the total aerobic expenditure. In a recent study, the VO2 consumed by healthy older persons during recovery from exercise exceeded that in the young by more than 30% (110). Although the precise causes of this greater VO2 use during recovery in the elderly is unclear, increased circulating catecholamine levels (111) and a higher core temperature that occur during exercise and early recovery in deconditioned older adults (112) may be contributory.

Because of the difficulty in imaging the heart during treadmill exercise, cycle ergometry has been used to dissect the relative contributions of cardiac factors in the age-associated decline in aerobic capacity (Table 2). During upright cycle ergometry, the peak VO2 of healthy BLSA participants averages about 80% of that during treadmill exercise, regardless of age. The primary factor limiting the duration and intensity of cycle exercise is usually leg fatigue. Peak cycle work rate and VO2 decline by ~50% between ages 20 and 90 years in healthy, nonathletic BLSA men and women, attributable to declines of ~30% in cardiac output and 20% in arteriovenous oxygen difference (Table 2) (113).

The age-associated decrease in cardiac index at maximal effort during upright cycle exercise (Fig. 11F) is due entirely to a reduction in heart rate (Fig. 11E), as the LVSVI does not decline with age in either gender (Fig. 11D) (114). However, the manner in which SVI is achieved during maximal exercise varies dramatically with aging. Although older individuals have a blunted capacity to reduce ESVI (Fig. 11B) and to increase ejection fraction (Fig. 11C), this deficit is offset by a larger EDVI (Fig. 11A) (114). Thus, a “stiff heart” that prohibits sufficient filling between beats during exercise does not
characterize aging in healthy individuals. The larger EDVI in healthy older versus younger individuals during vigorous aerobic exercise is due in part to a longer diastolic interval (i.e., slower heart rate) and to a greater amount of blood remaining in the heart at end systole (Fig. 11B) (114).

Given the accelerated decline in VO$_2$max with age, an important question is whether aerobic training of sedentary older adults can improve their CV reserve capacity. It has been amply documented that physical conditioning of older persons can substantially increase their maximum aerobic work capacity. In a recent meta-analysis of 41 trials in 2102 individuals aged 60 and older, aerobic training elicited a 16.3% mean increase in VO$_2$max (115). The extent to which this conditioning effect results from enhanced central cardiac performance versus augmented peripheral mechanisms, including changes in skeletal muscle mass, varies with the characteristics of the population studied, the type and degree of conditioning achieved, gender, body position during study, and likely genetic factors.

A longitudinal study of older men during upright cycle ergometry indicates that aerobic training enhances VO$_2$max in part by increases in the maximum cardiac output due to augmented maximum SV and in part by increasing the arteriovenous oxygen difference (116). The augmentation of maximum SV is due primarily to an augmented reduction of LVESV and, thus, a concomitant increase in LV ejection fraction; however, conditioning status had minimal effect on LVEDV during exercise in older adults. This contrasts with the effect of physical conditioning in younger persons, which substantially increases EDV and SV on the basis of the Frank-Starling mechanism, as well as via an enhanced LV ejection fraction. In contrast to the improved LV ejection post-training, the maximal heart rate of older (as well as younger) persons does not vary with conditioning status. Thus, physical conditioning of older persons does not appear to offset the age-associated deficiency in sympathetic modulation. Rather, increased LV ejection from aerobic training in this age group appears to derive from the reduction in vascular afterload, as reflected in a reduced pulse wave velocity (117) and carotid augmentation index, with possible contribution from augmented maximum intrinsic myocardial contractility. Furthermore, aerobic training in

### Table 2

| Changes in Maximal Aerobic Capacity and Its Determinants Between Ages 20 and 80 Years in Healthy Volunteers |
|--------------------------------------------------|-----------------------------------------------------|
| Oxygen consumption          | ↓ (50%)                                           |
| (A-V)O$_2$ difference        | ↓ (20%)                                           |
| Cardiac output              | ↓ (30%)                                           |
| Heart rate                  | ↓ (25%)                                           |
| Stroke volume               | no Δ                                               |
| Preload                      |                                                    |
| EDV                          | ↑ (30%)                                           |
| Afterload                    |                                                    |
| Vascular (SVR)              | ↑ (30%)                                           |
| Cardiac (ESV)               | ↑ (275%)                                          |
| Cardiac (EDV)               | ↑ (30%)                                           |
| Contractility                | ↓ (60%)                                           |
| Ejection fraction            | ↓ (15%)                                           |
| Plasma catecholamines        |                                                    |
| Cardiac and vascular        | ↑                                                   |
| Responses to β-adrenergic stimulation | ↓                                                 |

*Abbreviations: A-V, arteriovenous; EDV, end-diastolic volume; ESV, end-systolic volume; SVR, systemic vascular resistance.*

A longitudinal study of older men during upright cycle ergometry indicates that aerobic training enhances VO$_2$max in part by increases in the maximum cardiac output due to augmented maximum SV and in part by increasing the arteriovenous oxygen difference (116). The augmentation of maximum SV is due primarily to an augmented reduction of LVESV and, thus, a concomitant increase in LV ejection fraction; however, conditioning status had minimal effect on LVEDV during exercise in older adults. This contrasts with the effect of physical conditioning in younger persons, which substantially increases EDV and SV on the basis of the Frank-Starling mechanism, as well as via an enhanced LV ejection fraction. In contrast to the improved LV ejection post-training, the maximal heart rate of older (as well as younger) persons does not vary with conditioning status. Thus, physical conditioning of older persons does not appear to offset the age-associated deficiency in sympathetic modulation. Rather, increased LV ejection from aerobic training in this age group appears to derive from the reduction in vascular afterload, as reflected in a reduced pulse wave velocity (117) and carotid augmentation index, with possible contribution from augmented maximum intrinsic myocardial contractility. Furthermore, aerobic training in
Sedentary older adults reduced their oxygen debt immediately post-exercise by nearly 30%, translating into an 18% increase in exercise efficiency; in contrast, efficiency did not change in younger persons after training (110).

MECHANISMS OF IMPAIRED LV EJECTION DURING MAXIMAL AEROBIC EXERCISE IN HEALTHY OLDER ADULTS

The ejection fraction at maximal exercise and its increase from rest are sometimes used clinically as a diagnostic tool to detect and quantify the severity of cardiac disease, particularly CAD. Exercise ejection fraction is thus of considerable clinical interest. The impaired ability of healthy older men and women to reduce LV ESVI during vigorous

Figure 11  Scatter plots of left ventricular volumes (A, B), ejection fraction (C), stroke volume (D), heart rate (E), and cardiac index (F) during maximal graded upright cycle exercise in healthy BLSA volunteers, carefully screened to exclude silent coronary artery disease. Note the similar age changes in men and women and the increasing heterogeneity with age in the end-systolic volume index, ejection fraction, and heart rate. Abbreviation: BLSA, Baltimore Longitudinal Study of Aging. Source: Adapted from Ref. 114.
exercise accounts for their smaller increase in ejection fraction from rest and their lower maximal value compared to younger individuals (Fig. 11C) (114). A blunted LV ejection fraction response during exercise is even more prominent in older individuals with exercise-induced silent myocardial ischemia than in those without evident ischemia, due to a more pronounced inability to reduce ESVI (118).

The underlying mechanisms for the age-associated reduction in maximum ejection fraction are multifactorial and include (1) a reduction in intrinsic myocardial contractility, (2) an increase in vascular afterload, (3) arterial-ventricular load mismatching, and (4) a diminished effectiveness of the autonomic modulation of both LV contractility and arterial afterload. Although these age-associated changes in CV reserve per se are insufficient to produce clinical heart failure, they appear to lower the threshold for developing symptoms and signs of heart failure and adversely influence its clinical severity and prognosis for any level of disease burden (Table 1).

**Myocardial Contractility**

How aging affects factors that regulate intrinsic myocardial contractility in humans is incompletely understood because the effectiveness of intrinsic myocardial contractility in the intact circulation is difficult to separate from loading and autonomic modulatory influences on contractility. Given that the heart rate per se is a determinant of the myocardial contractile state, a deficit in maximal intrinsic contractility of older persons might be expected on the basis of their reduced maximum heart rate. Supporting evidence for reduced LV contractility with aging during stress comes from a study in which the LV of older but not younger healthy BLSA men dilated at end diastole in response to a given increase in afterload during β-adrenergic blockade (105).

Myocardial systolic stiffness or elastance, one index of LV contractile performance, is best approximated by the slope of the end-systolic pressure (ESP) on ESV coordinates measured across a range of EDVs at rest; this slope has not been determined in a healthy population across a broad age range and by convention cannot be accessed during exercise. A single point depicting ESP/ESV as a contractility index at each overall CV level of performance presents an age-associated pattern of myocardial contractile reserve that is nearly identical to the age-associated change in the pattern of ejection fraction in Figure 11C (114).

**LV Afterload**

Cardiac afterload has two components, one generated by the heart itself and the other by the vasculature. The cardiac component of afterload during exercise can be expected to increase slightly with age because the heart size increases in older persons throughout the cardiac cycle during exercise (114). The vascular load on the heart has four components: conduit artery compliance characteristics, reflected pulse waves, resistance, and inertance. Inertance is determined by the mass of blood in the large arteries that requires acceleration prior to LV ejection. As the central arterial diastolic diameter increases with aging (26,74), the inertance component of afterload likely increases. Thus, each of the pulsatile components of vascular load, measured at rest, increases with age.

Augmented LV afterload in older versus younger persons during exercise likely plays a major role in the failure of the acute LVESV reserve with advancing age. However, the extent to which the age-associated increases in afterload at rest becomes more pronounced during exercise is not known with certainty. Whereas the exaggerated cardiac dilation from the resting level that occurs during vigorous exercise in healthy older individuals suggests an exercise-induced increase in cardiac afterload, it has not
been possible to noninvasively assess PWV, augmentation index, aortic diameter, or impedance during exercise. Although some indices of afterload, such as arterial pressure and systemic vascular resistance, have been determined during exercise, their levels are confounded by the decrease in maximum exercise capacity that occurs with age.

**Arterial/Ventricular Load Matching**

Optimal ejection of blood from the heart occurs when ventricular and vascular loads are matched. The precise cardiac and vascular load matching that is characteristic of younger persons is thought to be preserved at older ages, at least at rest, because the increased vascular stiffness in older persons at rest is matched by increased resting ventricular stiffness (119).

For the ejection fraction to increase during exercise, the LV end-systolic elastance (ELV), i.e., the ESP/ESV ratio, must increase to a greater extent than the effective vascular elastance (EA), i.e., ESP/stroke volume. With increasing age, however, ELV fails to increase in proportion to the increase in EA; hence, the EA/ELV during exercise in older persons decreases to a lesser extent than it does in younger persons (120). This altered arterial-ventricular load matching in older versus younger persons during exercise is a mechanism for the deficit in the acute LV ejection fraction reserve that typically accompanies advancing age. Thus, the LV ejection fraction, often considered a measure of LV pump function, is determined by both cardiac and vascular properties, each of which changes with age.

Acute pharmacological reduction in both cardiac and vascular components of LV afterload by sodium nitroprusside infusions in older, healthy BLSA volunteers augments LV ejection fraction in these subjects at rest and throughout upright cycle exercise (121). Because of concomitant reductions in preload and afterload during sodium nitroprusside infusion, the LV of older persons delivers the same stroke volume and cardiac output as prior to infusion while working at a smaller size. In another study, acute infusion of the calcium channel blocker verapamil, which reduced exercise afterload but not preload, improved LV ejection and oxygen utilization during submaximal exercise in healthy older volunteers (119).

**Sympathetic Modulation**

During acute exercise and other stresses, sympathetic modulation of the CV system increases heart rate, augments myocardial contractility and relaxation, reduces LV afterload, and redistributes blood to working muscles and skin to dissipate heat. All of the factors that have been identified to play a role in the deficient CV regulation with aging, i.e., heart rate, afterload (both cardiac and vascular), myocardial contractility, and redistribution of blood flow, exhibit a deficient sympathetic modulatory component.

**Sympathetic Neurotransmitters**

Apparent deficits in sympathetic modulation of cardiac and arterial functions with aging occur in the presence of elevated neurotransmitter levels. Plasma levels of norepinephrine and epinephrine, during any perturbation from the supine basal state, increase to a greater extent in older than in younger healthy humans (83,111). This increase appears to be a compensatory response to the reduced cardiac β-receptor density with advancing age (122). The age-associated increase in plasma levels of norepinephrine results from an increased cardiac spillover into the circulation and, to a lesser extent, to reduced plasma clearance. Deficient norepinephrine reuptake at nerve endings has been suggested as the primary mechanism for increased spillover. During prolonged submaximal exercise, however, diminished neurotransmitter reuptake might also be associated with reduced
release and spillover in older adults (123), contributing to the age-associated deficit in cardioacceleration and LV systolic performance seen during such an exercise (124).

**Deficits in Cardiac β-Adrenergic Receptor Signaling**

The age-associated increase in neurotransmitter spillover into the circulation during acute stress implies a greater heart and vascular receptor occupancy by these substances. Experimental data indicate that this condition leads to desensitization of the postsynaptic signaling components of sympathetic modulation. The deficits in β-adrenergic signaling with aging are attributable in part to reduction in β-receptor numbers, deficient G-protein coupling of receptors to adenyl cyclase and, possibly, to age-associated reductions in the amount or activation of adenyl cyclase, leading to a relative reduction in the ability to augment cellular cAMP in response to β-receptor stimulation in the older heart.

Numerous studies support the concept that the efficiency of postsynaptic β-adrenergic signaling declines with aging (122). One line of evidence derives from the observation that acute β-adrenergic receptor blockade changes the exercise hemodynamic profile of younger persons to resemble that of older ones. Thus, the reduction in heart rate during exhaustive aerobic exercise in the presence of acute β-adrenergic blockade is greater in younger than in older subjects, and significant β-adrenergic blockade–induced LV dilatation occurs only in younger group (125). In addition, the age-associated deficits in early LV diastolic filling rate, both at rest and during exercise, are abolished by acute β-adrenergic blockade (90). However, acute β-adrenergic blockade causes SVI to increase to a greater extent in younger than in older individuals, due in part to the greater increase in LV filling time in the young, caused by greater reduction in their maximal heart rate (125).

When perspectives from intact humans to subcellular biochemistry in animal models are integrated, a diminished responsiveness to β-adrenergic modulation is among the most consistently observed CV changes that occur with advancing age. Age-associated alterations in CV function that exceed the identified limits for healthy elderly individuals most likely represent interactions of aging per se with severe physical deconditioning and/or CV disease, both of which are highly prevalent among older adults.

**RELEVANT AGING CHANGES IN OTHER ORGAN SYSTEMS**

Because of the close relationships between the CV system and other organs, it is important to recognize some of the more salient non-CV changes that occur with age. In the lungs, loss of elastic recoil causes reduced emptying and thus reduced vital capacity and minute ventilation during vigorous exercise. Plasma and total blood volumes decline moderately with age. Age-related loss of skeletal muscle mass, termed sarcopenia, is paralleled by reduced muscle strength, a major cause of disability and reduced quality of life in the elderly. A similar loss of bone occurs with age and is exacerbated by estrogen deficiency in postmenopausal women, leading to a marked increase in fracture risk. Additionally, age-associated nephrosclerosis results in loss of renal parenchyma and reductions in renal plasma flow, creatinine clearance, plasma rennin activity, and plasma aldosterone. These renal changes decrease the elimination of renally excreted drugs, attenuate responses to sodium restriction and volume expansion, and increase the risk for hyperkalemia. Although creatinine clearance typically declines by ~50% between the third and ninth decades, serum creatinine changes minimally because of the parallel loss of muscle mass.
ELECTROCARDIOGRAPHY AND ARRHYTHMIAS

Conduction System

The cardiac conduction system undergoes multiple changes with age that affect its electrical properties and, when exaggerated, cause clinical disease. A generalized increase in elastic and collagenous tissue commonly occurs. Fat accumulates around the sinoatrial node, sometimes creating partial or complete separation of the node from the atrial tissue. In extreme cases, this may contribute to the development of sick sinus syndrome. A pronounced decline in the number of pacemaker cells generally occurs after age 60; by age 75, less than 10% of the number seen in young adults remain. A variable degree of calcification of the left side of the cardiac skeleton, which includes the aortic and mitral annuli, the central fibrous body, and the summit of the interventricular system, is observed. Because of their proximity to these structures, the atrioventricular (A-V) node, A-V bifurcation, and proximal left and right bundle branches may be damaged or destroyed by this process, resulting in A-V or intraventricular block.

ELECTROCARDIOGRAPHY

Alterations in cardiac anatomy and electrophysiology with age often manifest themselves on the ECG. Because the resting EGG remains the most widely used cardiac diagnostic test, a review of these aging changes is relevant to distinguish them from those imposed by disease.

Sinus Node Function

Whereas supine resting heart rate is unrelated to age in most studies (Table 3; Fig. 12, upper panel), the phasic variation in R–R interval known as respiratory sinus arrhythmia declines with age (126,127). Similarly, a reduced prevalence of sinus bradycardia on resting ECG is evident by the fourth decade (126). Because both sinus arrhythmia and sinus bradycardia are indices of cardiac parasympathetic activity, the age-associated reduction in parasympathetic function (127) may mediate both findings. Spectral analysis of heart rate variability has confirmed an age-related reduction of high-frequency (0.15–0.45 Hz) oscillations indicative of vagal efferent activity (Fig. 12, lower panel) (128,129). Although physical conditioning status influences autonomic tone, a cross-sectional study in BLSA volunteers demonstrated that the deconditioning that usually accompanies the aging process plays only a minor role in the age-associated

Table 3 Normal Age-Associated Changes in Resting ECG Measurements

<table>
<thead>
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<th>Measurement</th>
<th>Change with age</th>
<th>Effect on mortality</th>
</tr>
</thead>
<tbody>
<tr>
<td>R–R interval</td>
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<td>None</td>
</tr>
<tr>
<td>P-wave duration</td>
<td>Minor increase</td>
<td>None</td>
</tr>
<tr>
<td>P-R interval</td>
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<tr>
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</tr>
<tr>
<td>QRS voltage</td>
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<tr>
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<td>Probable increase</td>
</tr>
<tr>
<td>T-wave voltage</td>
<td>Decrease</td>
<td>None</td>
</tr>
</tbody>
</table>
Patients with organic heart disease demonstrate a reduced respiratory sinus arrhythmia compared to age-matched normal individuals. A blunting of high-frequency oscillations in apparently healthy older volunteers is predictive of future coronary events and total mortality. Time domain indices of heart rate variability also decline substantially with age; the pattern of decline varies with the specific time domain measure. Younger men generally display higher time domain indices than younger women, but this gender difference narrows or disappears at older ages. In a Swiss population of healthy persons aged 50 years and older, CV risk factors, such as hypertension, smoking, non-high-density lipoprotein cholesterol, and C-reactive protein, were each associated with reduced heart rate variability during 24-hour ECG recordings.

On the resting ECG, sinus bradycardia below 50 bpm was found in 4.1% of 1172 healthy, nonendurance-trained, unmedicated participants aged 40 years and older from the BLSA; the prevalence was similar in men (3.9%) and women (4.5%) (134). Individuals with unexplained sinus bradycardia (mean age 58 years) had a significantly greater prevalence of associated conduction system abnormalities than nonbradycardic age- and sex-matched controls, but there was no difference in the incidence of future coronary events (angina pectoris, myocardial infarction, or cardiac death) over a 5.4-year mean

Figure 12 Mean RR interval (RRI) and respiratory sinus arrhythmia (RSA) during 3 min of sitting in healthy BLSA men (closed circles and dashed line) and women (open circles and solid line). Whereas RRI (top) was unrelated to age in either sex, RSA (bottom) declined similarly with age in women (r = 0.61; p < 0.001) and men (r = 0.59; p < 0.001). Abbreviation: BLSA, Baltimore Longitudinal Study of Aging. Source: From Ref. 129.
follow-up period (134). Sinus bradycardia due to sick sinus syndrome is seen almost exclusively in the elderly and probably derives in part from the marked decline in the number of pacemaker cells in the sinoatrial node. In the absence of organic heart disease, such bradycardia is not associated with increased cardiac mortality (134,135).

**P Waves**

Paralleling the echocardiographic increase in left atrial size, the prevalence of left atrial abnormality, defined by a negative P terminal force in lead V1 of at least 0.04 mm-s, increases with age. Among 588 institutionalized elderly, such a P terminal force was only 32% sensitive, although 94% specific, for echocardiographic left atrial enlargement (136). A small increment in P-wave duration of about 8 milliseconds from the third to seventh decades has been observed (137), presumably secondary to the modest increase in left atrial size. There does not appear to be any increase in ECG evidence of right atrial enlargement with age when individuals with significant chronic obstructive lung disease are excluded.

**P–R Interval**

With advancing age, the P–R interval undergoes a modest but significant prolongation (138–140). In a database of 46,129 persons with very low probability of CV disease, mean PR interval increased from 148 to 166 milliseconds in women and from 153 to 182 milliseconds in men between the third and ninth decades (138). An increase in P–R interval from 159 to 175 milliseconds in men and from 156 to 165 milliseconds in women occurred between the ages of 30 and 72 years in BLSA volunteers (139). By high-resolution signal-averaged surface ECGs, the prolongation of A-V conduction was localized proximal to the His bundle deflection, but within the P–R segment, presumably reflecting delay within the A-V junction. In seven older men with first-degree A-V block, there was a similarly located but more pronounced A-V junctional delay (112). Using the conventional upper limit of 0.20 seconds, the prevalence of first-degree A-V block in healthy older men is usually 3–4%, a prevalence severalfold greater than in young men (140). To reflect the age-associated slowing of A-V conduction, a value of 0.22 seconds has been proposed for the upper limit of normal P–R interval in persons over 50 years of age (140). Both cross-sectional and longitudinal studies have generally found no correlation between first-degree A-V block and cardiac disease (141) or mortality (142).

**QRS Complex**

Although the QRS duration shows no significant age relationship, the QRS axis shifts progressively leftward with age. In the database of 46,129 normals, there was a shift in the mean QRS axis from 56° to 8° between the third and ninth decades, with no gender difference (138). The corresponding lower normal limits shifted from −3° to −60°. Thus, the prevalence of left-axis deviation of less than −30° increases dramatically with age, reaching 20% by the tenth decade (143). This leftward QRS axis shift may be largely due to the age-related increase in LV wall thickness (74,75). Longitudinal studies have failed to demonstrate any increase in cardiac morbidity or mortality associated with this isolated ECG finding (144,145). In patients with known organic heart disease, however, left or right bundle branch block (BBB) portends a worse CV prognosis if left axis deviation is present (146).

Cross-sectional (147) and longitudinal (148) studies have demonstrated a decrease in R- and S-wave amplitudes with advancing age, evident by the fourth decade. At first glance,
this decrease in QRS amplitude seems paradoxical, given the age-related increase in LV thickness. However, the surface ECG is influenced by extracardiac as well as cardiac factors. By increasing the distance between the heart and the chest wall, senile kyphosis and pulmonary hyperinflation in older individuals may contribute to a decrease of QRS voltage.

Despite the age-related decline in mean QRS amplitude, the prevalence of electrocardiographic LV hypertrophy (LVH) increases with age (149), probably secondary to the high prevalence of hypertension, CAD, and degenerative aortic valvular disease in the elderly. Echocardiographic studies have demonstrated that the standard ECG is quite insensitive, although very specific, for anatomical LVH in older populations (150). In the Framingham study (149,150) and other older cohorts (123), ECG evidence of LVH was strongly related to the presence of hypertension and was a potent independent risk factor for future CV morbidity and mortality. Thus, the presence of ECG criteria for LVH in an older individual should normally trigger further diagnostic assessment, particularly echocardiography.

Left and right BBB both increase in prevalence with age (152–154); nevertheless, these conduction defects should not be attributed to aging per se. In older populations, left BBB occurs only about half as often as right BBB. In contrast to its right-sided counterpart, left BBB is uncommon in the absence of CV disease (155). The prognosis of left BBB therefore reflects that of the underlying heart disease. Whereas left BBB portended a more ominous prognosis than right BBB in Framingham men, the two conduction defects had similar prognostic significance in women (152,153). Among 310 predominantly middle-aged individuals with BBB and no apparent heart disease, both left BBB and right BBB increased in prevalence with age, but neither was associated with increased total mortality over a 9.5-year mean follow-up (155). A nonspecific intraventricular conduction defect exceeding 120 milliseconds occurred in only 1.9% of Framingham participants aged 70 years and older and, like left BBB, was strongly associated with clinical heart disease (156).

Complete right BBB was observed in 39 of 1142 men (3.4%) in the BLSA (157). Among the 24 individuals (mean age 64 years) without evidence of heart disease and for whom follow-up information was available, the incidence of angina, nonfatal myocardial infarction (MI), heart failure, advanced heart block, or cardiac death did not differ from those in age-matched controls over a mean observation period of 8.4 years. At long-term follow-up, maximal exercise capacity and maximal heart rate were similar to those of controls, although a higher prevalence of left-axis deviation was found in the group with right BBB (46% vs. 15%, respectively) (157). These findings suggest that right BBB in the absence of clinical heart disease is not rare in older men and reflects a primary abnormality of the cardiac conduction system. Women in the Framingham study demonstrated a lower prevalence of right BBB than men, but had a stronger association of this conduction defect with cardiomegaly and congestive heart failure (152).

Q waves in two or more contiguous ECG leads are generally considered evidence of prior MI. In older, as in younger, populations, such Q waves are usually associated with clinical heart disease and increased cardiac mortality. Indeed, pathological Q waves may serve as the initial clue to the presence of CAD. Prior studies have shown that 25–30% or more of acute infarctions are clinically silent (158–160). The incidence of such “silent” infarctions increases strikingly with age. Aronow et al. (160) reported that 68% of infarctions were silent in a geriatric chronic care facility. Despite the absence of symptoms, these silent MI’s portend a long-term risk of mortality similar to their symptomatic counterparts.

Among the elderly, Q waves commonly occur in the absence of CAD. A QS complex in leads 3 and a VF may occasionally result from marked left-axis deviation. A
pattern of poor R-wave progression in leads V₁ to V₃ is a normal age trend, because of the decrease in the initial 20 milliseconds anterior QRS vector with age (140). Such a pattern may also result from obesity, chronic obstructive lung disease, and LVH, all of which are common in older populations.

**Repolarization**

Abnormalities involving the ST segment and T wave probably constitute the most prevalent age-associated findings on the ECG. In a study of 671 persons aged 70 years and older, nonspecific ST–T changes were the most common ECG abnormalities, occurring in 16% of individuals (154). In this sample and others, repolarization abnormalities were generally associated with clinical heart disease. Such an association may stem in part from the frequent use of digitalis and various antiarrhythmic drugs by elderly cardiac patients. Much of the reported increased risk attached to these nonspecific repolarization changes is undoubtedly due to the underlying heart disease that necessitated use of these cardiac medications. Even among clinically healthy older persons, however, minor ST-segment sagging or straightening is relatively common, although of questionable prognostic significance.

A decrease in the T-wave amplitude with age begins by the fourth decade (140,147). The spatial T-wave vector shifts leftward with age in concert with the leftward shift in ORS axis. Obesity magnifies these changes in the T waves, especially in men (140). The isolated presence of flattened T waves, particularly in lead aVL, does not portend increased CV risk, at least in middle-aged samples (161). In contrast, definite T-wave inversion usually occurs in patients with organic heart disease and is associated with increased mortality.

ARRHYTMIAS

An increase in the prevalence and complexity of both supraventricular and ventricular arrhythmias, whether detected by resting ECG, ambulatory monitoring, or exercise testing, is a hallmark of normal human aging.

**Atrial Arrhythmias**

Isolated premature atrial ectopic beats (AEB) appear on the resting ECG in 5–10% of individuals older than 60 years and are not generally associated with heart disease. Isolated AEB were detected in 6% of healthy BLSA volunteers older than 60 years at rest, in 39%...
during exercise testing, and in 88% during ambulatory 24-hour monitoring (168). Such isolated AEB on ambulatory monitoring, even if frequent, were not predictive of increased cardiac risk in this sample over a 10-year mean follow-up period (169). Among 1372 predominantly healthy persons 65 years old in the CHS, isolated AEB were found in 97% and were frequent in 18% of women and 28% of men (Table 4) (170).

### Atrial Fibrillation

Atrial fibrillation (AF) is found in approximately 3–4% of subjects over age 60 years (Table 4), a rate 10-fold higher than the general adult population (170,171); the prevalence in octogenarians approaches 10% (172). Chronic AF is most commonly due to CAD and hypertensive heart disease, mitral valvular disorders, thyrotoxicosis, and sick sinus syndrome. The association between hyperthyroidism and AF is observed almost exclusively in the elderly (173); this arrhythmia may be the sole clinical manifestation of so-called apathetic hyperthyroidism in geriatric patients. In the Framingham population, AF without identifiable cause, so-called lone AF, represented 17% of men and 6% of women with AF, with mean ages of 70.6 and 68.1 years, respectively (174). Individuals with lone AF suffered over four times as many strokes as those in sinus rhythm during long-term follow-up, although their rates of coronary events or congestive heart failure were not increased (174). Atrial flutter is a rare arrhythmia in any age group and is usually associated with organic heart disease.

Several age-associated physiological changes contribute to the high prevalence of AF among the elderly. As noted above, left atrial size increases modestly with age, providing an augmented late diastolic filling rate that appears to compensate for the age-related reduction in early filling. Among adults aged ≥65 years, in Olmstead County, Minnesota, who underwent clinically indicated echocardiography, both a larger left atrial volume and impaired early diastolic LV function were independent predictors of nonvalvular AF (175). In addition, both left and right atrial wavefront propagation velocities show strong inverse correlations with age, increasing the likelihood for intra-atrial reentry to occur in older individuals (176).
Paroxysmal AF also increases strikingly with age. Among CHS participants in sinus rhythm, short runs of AF were seen in ~3% of individuals during 24-hour ambulatory ECG monitoring (Table 4) (170). In a series of persons with paroxysmal AF, the number and duration of abnormal atrial electrograms recorded during sinus rhythm increased with age (177). The incidence of postoperative AF, a major cause of morbidity and increased hospital costs, also rises steeply with age. Among 527 patients undergoing major elective thoracic surgery, age was the strongest predictor of postoperative AF; odds of this arrhythmia were increased 2.5-fold in persons ≥70 years old versus those <60 years (178). A recent study of 205 patients undergoing elective cardiac surgery demonstrated additive effects of age and left atrial volume on the seven-day incidence of postoperative AF (Fig. 13) (179).

Paroxysmal Supraventricular Tachycardia

Short bursts of paroxysmal supraventricular tachycardia (PSVT) on a resting ECG are found in 1–2% of normal individuals older than 65 years. Twenty-four-hour ambulatory monitoring studies have demonstrated short runs of PSVT (usually 3 to 5 beats) in 13–50% of clinically healthy older persons (Table 4) (168,170). Although the presence of nonsustained PSVT on ambulatory monitoring did not predict an increase in risk of future coronary events in BLSA participants, 2 of 13 individuals with PSVT later developed de novo AF, compared with only 1 of the 85 without PSVT (169). Exercise-induced PSVT has been observed in 3.5% of over 3000 maximal treadmill tests on apparently healthy BLSA volunteers (180). The arrhythmia increased sharply with age, from 0% in the twenties to approximately 10% in the eighties (Fig. 14A); similar to PSVT on ambulatory ECG, the vast majority of these episodes were asymptomatic 3- to 5-beat salvos. Coronary risk factors and ECG or thallium scintigraphic evidence of ischemia occurred with similar prevalence in the 85 volunteers with exercise-induced PSVT as in age- and sex-matched controls. Of importance, the group with PSVT experienced no increase in subsequent coronary events over a 5.5-year mean follow-up period. However, 10% of the individuals with PSVT later developed a spontaneous atrial tachyarrhythmia compared with only 2% of the control group, analogous to the results of the ambulatory 24-hour ECG (180).
Figure 14 Increased prevalence of exercise-induced cardiac arrhythmias with age during the initial maximal treadmill exercise test in BLSA volunteers free from clinical cardiac disease. The numbers above each bar represent the number of persons in each age decade by gender. (A) Prevalence of exercise-induced nonsustained SVT as a function of age and sex in 1383 apparently healthy individuals. The age-associated increase in SVT prevalence was more pronounced in men ($p < 0.001$) than in women ($p = 0.09$). (B) Prevalence of frequent or repetitive ventricular ectopic beats in 1160 clinically healthy volunteers. A highly significant increase in prevalence was observed with age in men but not in women. *Abbreviation:* BLSA, Baltimore Longitudinal Study of Aging; SVT, supraventricular tachycardia. *Source:* (A) From Ref. 180 and (B) from Ref. 193.
Ventricular Arrhythmias

Both in unselected populations and in those clinically free of heart disease, an exponential increase in the prevalence of ventricular ectopic beats (VEB) occurs with advancing age. Pooled data from nearly 2500 ECGs from hospitalized patients older than 70 years revealed VEB in 8% (181). Among apparently healthy BLSA volunteers with a normal ST-segment response to treadmill exercise, isolated VEB occurred at rest in 8.6% of men over age 60 years compared with only 0.5% in those 20 to 40 years old (182). Of note, the prevalence of resting VEB was not age related in women.

The prognostic significance of VEB detected on the resting ECG in the general elderly population is controversial. Significant increases in cardiac mortality among persons with VEB were observed in studies from Busselton (183) and Manitoba (184), with risk ratios of 3.3 and 2.4, respectively, compared with arrhythmia-free cohorts. The Framingham community, however, demonstrated no increase in the age-adjusted risk ratio for cardiac events (185). Data from the MRFIT (Multiple Risk Factor Intervention Trial) study suggest that the prognostic significance of resting VEB may vary according to age; asymptomatic white men under 50 years with frequent or complex VEB on a 2-minute resting rhythm strip suffered a 14-fold relative risk of sudden cardiac death, while in older men the risk was not significantly increased (186).

Twenty-four-hour ambulatory ECG recordings have demonstrated the presence of VEB in 69–96% of asymptomatic elderly (169,170,187,188). Not only the prevalence but also the density and complexity of VEB increase with age. In the CHS, VEB were found in 82% of 1372 subjects aged 65 years and older, including 7% with 3- to 5-beat runs of nonsustained ventricular tachycardia (VT). The prevalence of all VEB forms was higher in men than in women (Table 4) (170). Among 50 individuals older than 80 years without clinical heart disease, VEB were observed in 96%, including multifocal VEB in 18%, couplets in 8%, and nonsustained VT in 2% (187). In 106 predominantly healthy patients aged 75 years and above, Camm et al. detected VEB in 69% (188); VEB were multifocal in 22% and paired in 4% and occurred in short runs in 4%. Among 98 carefully screened asymptomatic BLSA participants older than 60 years, 35% had multifocal VEB, 11% VEB couplets, and 4% short runs of VT on 24-hour monitoring (168). The prevalence of simple and complex VEB in all of these studies is much higher than in series of healthy younger volunteers.

The prognostic importance of VEB detected on ambulatory monitoring, like those found on the resting ECG, is unclear. Over a 10-year mean follow-up period, 14 of the 98 older, carefully screened BLSA participants who underwent ambulatory ECG developed coronary events. The prevalence and complexity of VEB were virtually identical in the group that experienced an event and the group that did not (169). However, horizontal or slowly upsloping ST-segment depression on the ambulatory ECG predicted an increased risk of such events (169). In the series of Camm et al. (189), 92% of the five-year survivors who were initially free of VEB remained without VEB on the five-year follow-up recording. In contrast to the BLSA results, an almost doubled crude mortality was found among individuals with ≥10 VEB/hr versus those with fewer VEB. It should be noted that 83% of the Camm et al. volunteers were taking medications, including several patients with known heart disease. In a cohort of 456 Swedish men aged 68 years, frequent or complex VEB on 24-hour ECG were found in 35% of those without clinical coronary heart disease (CHD) and predicted increased risk of MI and CHD mortality over a 10.3-year mean follow-up (190).

Exercise testing elicits a striking increase in the prevalence and complexity of VEB with advancing age similar to that seen on the ambulatory ECG. In apparently healthy
BLSA volunteers, isolated VEB during or after maximal treadmill exercise increased in prevalence from 11% to 57% between the third and ninth decade (182). Although LV mass index and peak exercise systolic blood pressure were higher in subjects who developed exercise-induced VEB than in those who did not, by multivariate analysis only older age independently predicted the appearance of VEB (191). Asymptomatic exercise-induced runs of VT, all ≤6 beats in duration, were found in 4% of apparently healthy BLSA individuals aged 65 and older, a rate 25 times that of younger persons (192). Over a mean follow-up of about two years, however, none of these older volunteers with nonsustained VT during exercise testing developed angina, MI, syncope, or cardiac death.

In a subsequent BLSA analysis, of 1160 clinically healthy individuals who underwent an average of 2.4 maximal treadmill exercise tests per individual, 80 developed frequent VEB (≥10% of beats in any minute) or nonsustained VT on one or more tests (193). These 80 individuals were older than those free of such arrhythmias (64 vs. 50 years). Of note, the striking age-associated increase in occurrence of these complex exercise-induced VEB was observed only in men (Fig. 14B). The prevalence of coronary risk factors and exercise-induced ischemia by ECG and thallium scanning as well as the incidence of cardiac events (angina pectoris, nonfatal infarction, cardiac syncope, or cardiac death) was nearly identical in cases and controls matched for age and sex over a mean follow-up of 5.6 years without antiarrhythmic drug therapy (193). However, in a 23-year follow-up of 6101 French men aged 42 to 53 years and initially free of clinical CV disease, frequent VEB during exercise predicted a 2.5-fold increased risk of CV death, independent of standard coronary risk factors (194). Thus, the available data available in older adults without apparent heart disease support a marked age-related increase in the prevalence and complexity of exercise-related VEB, at least in men; however, the prognosis conferred by frequent or repetitive VEB induced by exercise in such individuals is unclear.

A factor of major importance in determining the prognostic significance of VEB in the elderly is the milieu in which they occur. For example, among 467 patients aged 62 to 101 years in a long-term care facility, complex VEB occurred during 24-hour ambulatory monitoring in 21% (195). In the subset without clinical heart disease, future coronary events developed in an identical 4% of those individuals with or without complex VEB; among patients with CAD, however, such events developed in 46% with complex VEB but only 23% of patients without them. A similar doubling of risk was seen in patients with hypertension, valvular disease, or cardiomyopathy who demonstrated complex VEB. Table 5 summarizes the effect of age on the prevalence of various cardiac arrhythmias and their relationship to mortality in apparently healthy older adults (196).

<table>
<thead>
<tr>
<th>Arrhythmia</th>
<th>Effect of age on prevalence</th>
<th>Effect on mortality^a</th>
</tr>
</thead>
<tbody>
<tr>
<td>Supraventricular ectopic beats</td>
<td>Increased</td>
<td>None</td>
</tr>
<tr>
<td>Paroxysmal supraventricular</td>
<td>Increased</td>
<td>Probably none</td>
</tr>
<tr>
<td>tachycardia</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Atrial fibrillation (chronic)</td>
<td>Increased</td>
<td>Increased</td>
</tr>
<tr>
<td>Ventricular ectopic beats</td>
<td>Increased</td>
<td>Probably none</td>
</tr>
<tr>
<td>Ventricular tachycardia (short runs)</td>
<td>Increased</td>
<td>Probably none</td>
</tr>
</tbody>
</table>

^aIn healthy elderly.
Normal Aging of the Cardiovascular System

In summary, aging is associated with multiple ECG changes in persons without evidence of CV disease. Such changes include a blunted respiratory sinus arrhythmia, a mild P–R interval prolongation, a leftward shift of the QRS axis, and increased prevalence, density, and complexity of ectopic beats, both atrial and ventricular. Although these findings generally do not affect prognosis in clinically healthy older adults, other findings that become more prevalent with age, such as increased QRS voltage, Q waves, QT interval prolongation, and ST–T-wave abnormalities, are generally associated with increased CV risk. Abnormalities such as left BBB or AF are strongly predictive of future cardiac morbidity and mortality among older adults, even if asymptomatic. A guiding principle for the practitioner is that the prognosis associated with a given ECG abnormality in the elderly is more strongly related to the presence and severity of underlying CV disease than to the ECG finding itself.

The views expressed in this chapter are those of the authors and do not necessarily represent those of the National Institutes of Health or the Department of Health and Human Services.

REFERENCES

Normal Aging of the Cardiovascular System

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Echocardiographic Measurements in Elderly Patients Without Clinical Heart Disease

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INTRODUCTION

The ability to image cardiac structures and to assess left ventricular (LV) function noninvasively has made echocardiography extremely useful in the evaluation of individuals with known or suspected heart disease. The noninvasive character of the ultrasound technique has made it particularly applicable to an older population (1,2). The goals of this chapter are to (1) discuss the effect of aging on LV systolic and diastolic function by M-mode and Doppler echocardiography and (2) present normative M-mode and Doppler echocardiographic measurement data that can serve as a basis for evaluating cardiac structure and function in elderly individuals.

This chapter presents data derived from (1) Doppler measurements of aortic flow velocity, used to evaluate LV systolic performance at rest and during exercise, and (2) transmitral flow velocity measurements, used to assess LV diastolic function at rest.

RELATIONSHIP OF AGE TO NORMAL M-MODE ECHOCARDIOGRAPHIC MEASUREMENTS

To determine the relationship between age and M-mode echocardiographic measurements in normal subjects, we studied 136 adults (78 men and 58 women), aged 20 to 97 years, without evidence of cardiovascular disease (CVD) (3). These subjects all underwent a comprehensive medical history and physical examination, chest roentgenography, electrocardiography, and M-mode echocardiography. In no subject did this evaluation reveal the presence of heart disease, hypertension, other serious illness, or obesity.
Furthermore, all subjects had a normal electrocardiogram (ECG), normal chest film, and no evidence of mitral valve prolapse or pericardial effusion on M-mode echocardiogram.

M-mode echocardiography was performed in the left lateral decubitus position, and the following measurements were made: LV internal dimensions at end diastole (LVIDd) and end systole (LVIDs); ventricular septal (VSd) and posterobasal LV free-wall thickness (LVPWd) at end diastole; LVTDd, left ventricular transverse dimension measured during diastole; LVTDs, left ventricular transverse dimension measured during systole. Source: From Ref. 71.

Figure 1  Echocardiographic recording of the left ventricle showing parameters of left ventricular muscle mass and percentage fractional shortening. Abbreviations: VSd, inteventricular septal thickness measured during diastole; LVTDd, left ventricular transverse dimension measured during diastole; LVTDs, left ventricular transverse dimension measured during systole. Source: From Ref. 71.

Furthermore, all subjects had a normal electrocardiogram (ECG), normal chest film, and no evidence of mitral valve prolapse or pericardial effusion on M-mode echocardiogram.

M-mode echocardiography was performed in the left lateral decubitus position, and the following measurements were made: LV internal dimensions at end diastole (LVIDd) and end systole (LVIDs); ventricular septal (VSd) and posterobasal LV free-wall thickness (LVPWd) at end diastole; aortic root and left atrial dimensions; and mitral valve E-F slope, which corresponds to the rate of early diastolic closure of the anterior mitral valve leaflet (Fig. 1). In addition, LV mass, ejection fraction, and fractional shortening were derived from the following formulas (4):

\[
\text{LV mass} = [(1.05)(\text{LVID}_d + \text{VS}_d + \text{LVPW}_d)^3 - (\text{LVID}_d)^3]
\]

(1)

\[
\text{LV ejection fraction} = \frac{(\text{LVID}_d)^3 - (\text{LVID}_s)^3}{(\text{LVID}_d)^3} \times 100\%
\]

(2)

\[
\text{LV \% fractional shortening} = \frac{(\text{LVID}_d) - (\text{LVID}_s)}{(\text{LVID}_d)} \times 100\%
\]

(3)
In the absence of localized disorders of LV function like those that may be present in coronary artery disease, M-mode echocardiographic estimates have been reported to correlate well with two-dimensional echocardiographic and angiographic measurements of LV volume and ejection fraction (4). Also, under these conditions, LV percentage fractional shortening gives information similar to that obtained from LV ejection fraction. Although ejection fraction does not perfectly characterize the functional state of the LV, this measurement is accepted as providing an overall assessment of pump performance. Furthermore, ejection fraction is thought to be a more sensitive measurement of myocardial contractile state than either cardiac output or LV end-diastolic pressure.

Echocardiographic measurements were analyzed for the influence of age, sex, and body surface area (BSA). When the data for each echocardiographic parameter were analyzed separately for men and women as a function of BSA, statistically significant differences were found for three parameters: (1) ventricular septal thickness, (2) posterobasal free-wall thickness, and (3) estimated LV mass. However, since the sex differences for these three parameters were relatively small (range, 6.2–7.2%), we chose for the sake of simplicity to combine data for men and women in our calculation of regression equations and prediction intervals (3,5,6).

When patients were subdivided into six age groups, progressive changes were found in mean normal values for various M-mode echocardiographic parameters (Fig. 2). Specifically, when the older group (over 70 years) was compared with the youngest group (21–30 years), significant \( p < 0.01 \) increases in aortic root (22%) and left atrial (16%) dimensions, ventricular septal (20%) and LV free-wall (18%) thicknesses, and estimated LV mass (15%) were noted (3,5,6). In addition, a significant \( p < 0.01 \) decrease in mean mitral E–F slope (43%) and slight decreases in mean LV systolic and diastolic internal dimensions (5% and 6%, respectively; \( p < 0.05 \)) were noted. LV ejection fraction and

Figure 2  Percentage change in M-mode echocardiographic measurements in five older age groups compared with the 21- to 30-year age group. Data are displayed for AO, LA, LVWT, EJ FRACT, LVID\(_d\), and mitral E–F slope. Abbreviations: AO, aortic root dimension; LA, left atrial dimension; LVWT, left ventricular posterobasal free-wall thickness in diastole; EJ FRACT, LV ejection fraction; LVID\(_d\), LV internal dimension in diastole.
percentage fractional shortening were independent of age. These data were used to derive regression equations related to both age and BSA. The regression equations can be used to calculate mean normal values and 95% prediction intervals for echocardiographic measurements in adults.

We analyzed our data according to the general regression equation

\[
\text{Echo parameter} = B(\text{BSA}) + A \pm C,
\]

where \( A \) represents the intercept, \( B \) represents a slope unique for each parameter, and \( C \) represents the width of the 95% prediction interval; that is, the interval into which, with 95% confidence, a new normal observation would be expected to fall (3). When subjects were subdivided into six age groups, the slope of the regression relationship was found to be independent of age for every parameter (\( p > 0.05 \)), whereas the intercept showed significant variation with age for every parameter (\( p < 0.05 \)). Therefore, we assumed that the intercept \( A \), but not the slope \( B \), was influenced by age and that the width of the 95% prediction interval \( C \) was constant and not appreciably influenced by age or BSA. The values of \( A \) derived from our data for each age group are given in Table 1, which also includes the values of \( B \) and \( C \) for each parameter (3).

Figures 3 through 7 depict the relationships between age and aortic root dimension, left atrial dimension, LV diastolic and systolic dimension, LV posterior wall thickness, and LV mass. For each figure, the regression equations in Table 1 have been utilized to adjust the values to three representative BSA values (1.4, 1.8, and 2.2 m²) (3).

Our echocardiographic findings are compatible with information derived from previous studies using other methods. Roberts and Perloff noted that hearts of older individuals studied at necropsy appear to have smaller ventricular chambers and thicker walls than those of their younger counterparts (7). Although the magnitude of the decrease was small, we also noted that the internal dimensions of the LV decreased as age increased. We also noted progressive increases in the thickness of the ventricular septum and the LV free wall with increasing age. The magnitudes and rates of increase were similar for the septum and free wall, so that there was no change in the septum–free-wall

<table>
<thead>
<tr>
<th>Table 1</th>
<th>Regression Equations of Echocardiography Measurements Vs. Age</th>
</tr>
</thead>
<tbody>
<tr>
<td>Equation</td>
<td>Intercept (age dependent)</td>
</tr>
<tr>
<td>Equation</td>
<td>21–30</td>
</tr>
<tr>
<td>LVIDd</td>
<td>6.94 (BSA) +</td>
</tr>
<tr>
<td>LVIDs</td>
<td>4.24 (BSA) +</td>
</tr>
<tr>
<td>Septum</td>
<td>2.53 (BSA) +</td>
</tr>
<tr>
<td>LVPW</td>
<td>2.18 (BSA) +</td>
</tr>
<tr>
<td>LV mass</td>
<td>124 (BSA) +</td>
</tr>
<tr>
<td>Ao</td>
<td>8.31 (BSA) +</td>
</tr>
<tr>
<td>LA</td>
<td>9.98 (BSA) +</td>
</tr>
<tr>
<td>E-F slope</td>
<td>20.1 (BSA) +</td>
</tr>
</tbody>
</table>

**Abbreviations:** Ao, aortic root dimension; BSA, body surface area; LA, left atrial dimension; LVID, left ventricular internal dimension; \( d \), diastolic; \( s \), systolic.

**Source:** From Ref. 3.
Figure 3  Aortic root dimension in late diastole in millimeters versus age in years. In Figures 3 through 7, the mean value for each age group is depicted by a circle plotted at the mean age in the age group. The bracketed and shaded area on either side of the circle represents the 95% prediction interval for normal values for a subject with a BSA of 1.8 m². The 95% prediction intervals are also shown for subjects with BSA values of 1.4 m² (dotted lines) and 2.2 m² (solid lines). Abbreviation: BSA, body surface area. Source: From Ref. 3.

Figure 4  Left atrial dimension in late diastole in millimeters versus age in years. For each age group, the mean and 95% prediction interval for normal values are depicted. Source: From Ref. 3.
Figure 5  Left ventricular end-diastolic and end-systolic dimensions in millimeters versus age in years. For each age group, the mean and 95% prediction interval for normal values are depicted. Source: From Ref. 3.

Figure 6  Left ventricular posterior wall thickness in late diastole in millimeters versus age in years. For each age group, the mean and 95% prediction interval for normal values are depicted. Source: From Ref. 3.
Estimated left ventricular mass in grams versus age in years. The mean and 95% prediction interval are depicted for each age group. Source: From Ref. 3.
In our studies, LV ejection fraction and percentage fractional shortening did not change appreciably as age increased from 20 to 97 years. These findings are consistent with several previous studies (11,12), including one in which LV function was assessed with radionuclide cineangiography (11). If the LV internal dimension at end diastole is mildly reduced in older subjects, while ejection fraction and heart rate are unchanged, stroke volume and cardiac output at rest are expected to diminish slightly with advancing age. Data confirming this inference have been reported using a dye-dilution technique (13,14).

Our findings relating changes in echocardiographic parameters to increasing age are generally in agreement with findings reported by Gerstenblith et al. (15). The major difference is that we found a slight but significant decrease in LV systolic and diastolic internal dimensions with increasing age, whereas Gerstenblith and associates found no change. Importantly, women were not included in their study population, nor did they report measurements of left atrial dimension or LV mass. More recently, Shub et al. found increased LV mass to be associated with increasing age among women, but not among men (16). This variation may have been due to increasing body mass index with age among women only.

Findings from the Framingham Heart Study showed that age, height, systolic blood pressure, and body mass index were significant independent predictors of LV mass in 2226 men and 2746 women aged 17 to 90 years (17). However, when persons with (1) evidence of cardiopulmonary disease by history, physical examination, ECG, chest X ray, or echocardiogram; (2) systemic arterial blood pressure of at least 140/90 mmHg at the time of echocardiography; (3) use of prescription medications for cardiopulmonary disease; or (4) body weight ≥20% above or below the midpoint of recommended weight for height were excluded from the analyses, age was no longer a significant correlate of LV mass/height among 345 men and 517 women aged 20 to 79 years (18). These disparate findings suggest that increases in LV mass associated with age are likely confounded by risk factors that are associated with age, specifically obesity, hypertension, and clinically manifest cardiopulmonary disease.

Although it is highly likely that the echocardiographic changes reported in the different age groups are related to the aging process, longitudinal studies are needed to document these changes in serial studies in the same patient. Nonetheless, it is clear that normal echocardiographic values corrected for both age and BSA (or another measure of body size) should be used when evaluating adult patients suspected of having heart disease.

**RELATIONSHIP OF AGE TO LV SYSTOLIC PERFORMANCE AS MEASURED BY DOPPLER AORTIC FLOW VELOCITY PARAMETERS**

Doppler flow velocity measurements in the aorta have been shown to be useful in differentiating normal subjects from those with LV dysfunction (19,20). For example, patients with dilated cardiomyopathy demonstrate aortic peak flow velocities, flow velocity integrals, and average accelerations that are markedly reduced compared with those in normal subjects (Fig. 8) (19). Furthermore, in patients with heart failure receiving vasodilator therapy, changes in Doppler aortic peak flow velocity and flow velocity integral have been shown to be useful in estimating changes in systemic vascular resistance and stroke volume, respectively (20).

We evaluated the relationship between age and Doppler aortic flow velocity measurements in 97 adults (45 men and 52 women, aged 21–78 years) without clinical
No subject had a history of hypertension or CVD, and all had a normal cardiac examination, ECG, chest X-ray, and M-mode and two-dimensional echocardiogram.

Figure 8 demonstrates an aortic flow velocity recording from a normal subject (21,22). Peak flow velocity was measured in centimeters per second at the midpoint of the darkest area of the spectrum at the time of maximum flow velocity. Ejection time (ET) was measured in milliseconds from the onset of the systolic flow velocity curve to the time the curve crossed the zero-flow line at end systole. Aortic flow velocity integral (centimeters), which represents the area under the flow velocity curve, was estimated by the following formula (20):

\[
\text{Flow velocity integral} = 0.5 \times \text{peak flow velocity} \times \text{ET}
\]

Multiple linear regression analysis revealed that age was significantly correlated with aortic peak flow velocity, average acceleration, and flow velocity integral (all \( p < 0.001 \)) (22). Figure 9 depicts the relationship between aortic peak flow velocity and age. The two parameters were related by the following regression equation:

\[
\text{Aortic peak flow velocity} = -0.6(\text{age}) + 110 \ (r = -0.54; p = .001)
\]

Aortic peak flow velocity was significantly lower in the 61- to 70-year age decade (mean ±SD = 93 ± 11 cm/sec) than in the younger age group. (22). The correlation of aortic peak flow velocity with age remained significant (\( p < 0.001 \)) after division of peak flow
velocity by the square root of the R–R interval. More recently, Turkish investigators have also noted that aortic blood flow velocity was related to age \((p < 0.001)\) in both men and women \((9)\).

Figure 10 depicts the relationship between aortic flow velocity integral and age. Note the significantly lower \((p < 0.001)\) aortic flow velocity integral in the 61- to 70-year age decade (mean ± SD = 9.5 ± 2.3 cm) compared with the 21- to 30-year age decade (13.8 ± 2.1 cm). Aortic flow velocity integral and age are related by the following regression equation \((22)\):

\[
\text{Aortic flow velocity integral} = -0.09(\text{age}) + 16.5 \quad (r = -0.44; p < .001)
\]

The correlation with age remained significant \((p < 0.01)\) after correction of aortic flow velocity integral for the square root of the R–R interval.

The decreases in aortic peak flow velocity and flow velocity integral noted with increasing age are probably due, at least in part, to the increases in aortic root diameter noted with aging \((3,5,8,15)\). It has previously been shown that resting stroke volume \((3,5)\) and cardiac output \((23)\) do not change significantly with aging. Since Doppler stroke volume can be estimated by multiplying the aortic flow velocity integral by the aortic root area, it follows that a decrease in flow velocity integral must be accompanied by an increase in aortic root area (and diameter) to maintain a constant stroke volume. Furthermore, since the aortic flow velocity integral is approximately equal to \(1/2(\text{peak flow velocity}) \times \text{ejection time} \) \((20)\), and since aortic ejection time did not change with aging in this study, it follows that aortic peak flow velocity decreases with aging.

We found no significant differences in Doppler aortic flow velocity measurements between men and women of the same age. Furthermore, there was no significant
the relationship between BSA or blood pressure and any of the aortic flow velocity parameters in this group of normal subjects (22).

**RELATIONSHIP OF AGE TO LV SYSTOLIC PERFORMANCE WITH UPRIGHT EXERCISE AS MEASURED BY DOPPLER AORTIC FLOW VELOCITY RECORDING DURING TREADMILL TESTING**

To evaluate the effect of upright exercise on aortic peak flow velocity and acceleration, 60 normal subjects, aged 15 to 74 years, were evaluated by continuous-wave Doppler during treadmill stress testing using the Bruce protocol (24). Subjects were divided into three age groups, each with 20 subjects: group I, 21 ± 4 years (mean ± SD); group II, 36 ± 5 years; and group III, 58 ± 7 years. Periodic measurements of heart rate, blood pressure, and Doppler blood flow velocity and acceleration were made before, during, and after exercise. Continuous-wave Doppler measurements were recorded from the suprasternal notch. The relationship between Doppler aortic measurements and age, gender, heart rate, and blood pressure responses during exercise were evaluated.

Age alone was significantly related (inversely) to immediate postexercise Doppler aortic peak blood flow velocity (group I, 1.1 ± 0.2; group II, 1.0 ± 0.2; and group III, 0.8 ± 0.2 m/sec, respectively; $p < .01$) and peak acceleration (group I, 55 ± 15; group II, 46 ± 11; and group III, 36 ± 9 m/sec$^2$; $p < .05$) (Figs. 11 and 12). Gender, heart rate, and blood pressure changes during exercise, as well as exercise preconditioning, had no significant effect on these aortic flow characteristics.

These findings suggest that age is an important factor influencing aortic peak blood flow velocity and acceleration with exercise, as well as at rest. These changes in peak

**Figure 10** Relationship between aortic flow velocity integral (cm) and age (years). Note the significantly lower flow velocity integral in the 61- to 70-year age group than in the 21- to 30-year age group ($p < 0.001$). Source: From Ref. 18.
Figure 11 Doppler peak aortic blood flow velocity measurements before, during, and immediately after exercise. Data are shown as the mean for 20 subjects in each of the three groups, except as noted by \( n \) value in exercise stages III and IV. Abbreviations: Su, supine; St, standing; PO, immediate postexercise; P5, 5 minutes after exercise. Source: From Ref. 20.

Figure 12 Doppler peak acceleration measurements before, during, and immediately after exercise. Abbreviations and data display are as in Figure 11. Source: From Ref. 20.
velocity and acceleration with exercise may reflect, in part, changes in exercise LV function with age. Earlier studies (25–27) showed close correlations between these flow parameters and muscle contractility. However, alterations in aortic configuration, size, and compliance, as well as impedance (afterload), likely affect these Doppler parameters to a significant degree. Importantly, these age-dependent changes must be taken into account when using Doppler-determined peak velocity and acceleration in evaluating LV performance.

**RELATIONSHIP OF AGE TO GLOBAL LV DIASTOLIC FUNCTION AT REST AS EVALUATED BY DOPPLER TRANSMITRAL FLOW VELOCITY MEASUREMENTS**

Although LV systolic function is generally maintained with aging in healthy subjects (23), alterations in diastolic function are known to occur with “normal” aging (28,29). We evaluated the relationship between age and pulsed Doppler transmitral flow velocity measurements in 66 adult men and women, aged 21 to 78 years, without a history of hypertension or CVD (29). Measurements of early and late diastolic transmitral peak flow (filling) velocities, flow times, and flow velocity integrals, and early diastolic flow acceleration and deceleration were made at the level of the mitral leaflet tips. As shown in Figure 13, transmitral peak flow velocities in centimeters per second were measured in early and late diastole (i.e., at the time of atrial systole) at the midpoint of the darkest portion of the spectrum at the time of peak flow velocity.

Differences in Doppler transmitral flow velocity patterns between 30-year-old and 63-year-old normal adults are depicted in Figure 14 (29). Mitral peak flow velocity in early diastole (PFVE) was significantly lower \((p < 0.01)\) in the 61- to 70-year age decade \((45 \pm 10 \text{ cm/sec})\) than in the 21- to 30-year age decade \((66 \pm 11 \text{ cm/sec})\) (Fig. 15). Mitral peak flow velocity in late diastole (PFVA) was significantly higher \((p < .05)\) in the 61- to 70-year age decade \((55 \pm 11 \text{ cm/sec})\) than in the 21- to 30-year age decade \((41 \pm 7 \text{ cm/sec})\) (Fig 16). Mitral A/E ratio (i.e., PFVA/PFVE) was significantly higher \((p < 0.01)\) in the oldest \((1.2 \pm 0.3)\) than in the youngest \((0.6 \pm 0.1)\) age group (Fig. 17). Early diastolic flow time increased with age \((r = 0.36, p < 0.001)\), whereas the rate of early diastolic deceleration decreased with age \((r = -0.59, p < 0.001)\).

The results of this study demonstrate that aging is associated with progressive decreases in early diastolic transmitral peak flow velocity and early diastolic deceleration and progressive increases in late diastolic transmitral peak flow velocity and the ratio of late to early diastolic peak flow velocities. These findings are similar to those reported by Miyatake and associates (28).

Evidence that the decrease in early diastolic transmitral peak flow velocity is related to impaired early diastolic LV filling has been provided by several studies. Dabestani et al. (30) showed in 10 patients who underwent both Doppler mitral flow velocity recordings and videodensitometric analysis of LV filling from digital subtraction left ventriculograms that the percentage of total filling completed by mid-diastole was directly related to the early diastolic peak flow velocity measured by Doppler. These findings suggest that Doppler measurements of peak flow velocity in early diastole are related to the rate of ventricular filling. Rokey et al. (31) also reported a significant correlation between early diastolic transmitral peak flow velocity and angiographic peak filling rate \((r = 0.64)\). They noted even better correlations between Doppler echocardiographic and angiographic peak filling rates \((r = 0.87)\).
Miyatake et al. (28) postulated that the increase in late diastolic peak transmitral flow velocity with aging reflects an augmentation of ventricular filling by atrial contraction that compensates for decreased early diastolic ventricular filling. Our study demonstrated not only age-related increases in late diastolic peak flow velocity, but also in late diastolic flow time and flow velocity integral (29). These findings provide further evidence for an age-related increase in the contribution of atrial systole to ventricular filling.

**Figure 13** Normal flow velocity recording at the level of the mitral valve from the apical four-chamber view depicting the method for making Doppler measurements. Mitral PFVE and PFVA were measured (cm/sec) at the midpoint of the darkest portion of the spectrum at the time of the maximal flow velocity in early and late diastole, respectively. EDFT, ADFT, and EFDF were measured as noted. **Abbreviations:** PFVE, peak flow velocity in early diastole; PFVA, peak flow velocity in late diastole; EDFT, early diastolic flow time; ADFT, late diastolic flow time; EFDF, early diastolic deceleration time. **Source:** From Ref. 25.
Figure 14  Doppler mitral valve flow velocity recordings from a younger normal subject, age 30 (left), and from an older normal subject, age 63 (right). Note that the peak flow velocity in early diastole is lower and the late diastolic peak flow velocity is higher in the older subject than in the younger normal subject. Source: From Ref. 25.

Figure 15  Data for mitral PFVE (cm/sec) is displayed on the vertical axis versus age in years on the horizontal axis (n = 66). Note the negative slope of the regression equation PFVE = -0.52 (age) + 79. The correlation coefficient r = -0.55. Abbreviation: PFVE, peak flow velocity in early diastole. Source: From Ref. 25.
Figure 16 Data for mitral PFVA (cm/sec) is displayed versus age in years \((n = 66)\). Note the positive slope of the relationship, mitral PFVA = 0.39 (age) + 27. Abbreviation: PFVA, peak flow velocity in late diastole. Source: From Ref. 25.

Figure 17 Data for mitral A/E ratio is depicted versus age in years. Note the positive slope of the relationship, mitral A/E ratio = 0.016 (age) + 0.13. Source: From Ref. 25.
It may be that the position of the sample volume (tips of the leaflets or at the annulus) affects the relationship between age and diastolic function. Mantero et al. showed that the E-wave peak velocity at the mitral annulus was more strongly correlated with age than the velocity obtained at the tips of the mitral leaflets among 288 normal subjects aged 20 to 80 years (32). However, A-wave peak velocity at the leaflet tips was more strongly related to age than at the annulus. Similar results were found for the partial integrals of the E and A waves. We have previously shown that peak E- and A-wave velocities are both significantly higher (by about 20%) when measured at the leaflet tips than at the annulus (33).

It is now well-established that pulsed Doppler recordings of pulmonary venous flow patterns can be useful in evaluating LV diastolic function and in classifying LV diastolic dysfunction into stages (e.g., abnormal relaxation, “pseudonormal,” and “restrictive filling”). However, in using pulmonary venous flow patterns, it is important to appreciate that these flow patterns may also be dependent on age in healthy subjects (Fig. 18) (34). Gentile et al. reported significant correlations between age and peak systolic flow velocity ($r = 0.5; p < 0.001$) and its integral ($r = 0.5; p < 0.001$), and peak diastolic flow velocity ($r = -0.6; p < 0.001$) and its integral ($r = -0.44; p < 0.001$), but not the atrial reversal wave ($r = 0.1; p > 0.05$) among 143 normal subjects aged 20 to 80 years (35). Among 85 of 117 healthy volunteers with adequate tracings, Klein et al. found that those aged 50 years and older had increased pulmonary venous peak systolic flow velocity (71 ± 9 vs. 48 ± 9 cm/sec; $p < 0.01$), decreased diastolic flow velocity (38 ± 9 vs. 50 ± 10 cm/sec; $p < 0.01$), and increased peak atrial reversal flow velocity (23 ± 4 vs. 19 ± 4 cm/s; $p < 0.01$) compared with those younger than 50 years (36). Klein et al. later reported that the difference in duration of pulmonary venous atrial flow reversal and transmitral A-wave flow, previously related to LV end-diastolic pressure among patients with heart disease (37), was unrelated to aging in 72 healthy volunteers aged 23 to 84 years ($r = -0.16$) (38).

**RELATIONSHIP OF AGE TO SYSTOLIC AND DIASTOLIC MYOCARDIAL FUNCTION AS EVALUATED BY TISSUE DOPPLER VELOCITY, STRAIN, AND STRAIN RATE**

Newer applications of pulsed Doppler have allowed assessment of regional myocardial function in systole and diastole. These applications are based on recording pulsed tissue Doppler velocity, strain, and strain rate and displaying the tissue Doppler information in a gray-scale or color format.
Tissue Doppler Velocity

Color M-mode tissue Doppler imaging is an accurate method to assess the nonuniformity of transmural myocardial velocities and can be used for evaluating the impact of age on the different myocardial layers (39). As shown in Table 2, (40) the distribution of myocardial velocity across the myocardium is asymmetrical, with higher velocities in the subendocardium compared with the subepicardium. Moreover, this observation holds true for peak systolic, peak early diastolic, and peak late diastolic myocardial velocity. These data have been confirmed by myocardial velocity gradient curves across a broad age range. Sabbah et al. (41) reported that the maximal rate of systolic thickening of the total ventricular wall was higher than the maximal rate of systolic thickening of the epicardium. A previous report from Palka and associates, who used tissue Doppler myocardial velocities to study healthy subjects, also concluded that the subendocardium moves faster than the subepicardium during LV rapid filling (42).

Several possible explanations for this phenomenon have been suggested. Models of LV wall mechanics have demonstrated that the orientation of cardiac fibers, which is heterogeneous in the normal heart, determines the distribution of fiber strain during ejection (43). Greater dimensional changes in the subendocardium during systole are also

Table 2  Early Diastolic, Late Diastolic, and Systolic Myocardial Velocities (by Myocardial Layer) Vs Age Group

<table>
<thead>
<tr>
<th>Age Group</th>
<th>18–25 yr</th>
<th>26–45 yr</th>
<th>46–65 yr</th>
<th>66–94 yr</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>(n = 9)</td>
<td>(n = 23)</td>
<td>(n = 22)</td>
<td>(n = 13)</td>
</tr>
<tr>
<td>Early diastole</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Peak endocardial ED velocity</td>
<td>-13.85 ± 3.19</td>
<td>-13.58 ± 2.89</td>
<td>-9.25 ± 1.57</td>
<td>-6.06 ± 1.91</td>
</tr>
<tr>
<td>Peak mesocardial ED velocity</td>
<td>-9.71 ± 2.73</td>
<td>-10.29 ± 3.00</td>
<td>-7.47 ± 1.88</td>
<td>-4.98 ± 1.33</td>
</tr>
<tr>
<td>Peak epicardial ED velocity</td>
<td>-6.41 ± 2.16</td>
<td>-7.05 ± 2.55</td>
<td>-4.93 ± 1.50</td>
<td>-4.02 ± 1.16</td>
</tr>
<tr>
<td>Peak ED MVG</td>
<td>-11.01 ± 2.34</td>
<td>-9.72 ± 1.90</td>
<td>-6.58 ± 2.35</td>
<td>-3.46 ± 1.33</td>
</tr>
<tr>
<td>Late diastole</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Peak endocardial LD velocity</td>
<td>-2.16 ± 1.46</td>
<td>-2.85 ± 1.46</td>
<td>-4.37 ± 1.71</td>
<td>-5.95 ± 2.74</td>
</tr>
<tr>
<td>Peak mesocardial LD velocity</td>
<td>-1.71 ± 1.40</td>
<td>-2.34 ± 1.40</td>
<td>-3.62 ± 1.61</td>
<td>-5.32 ± 2.41</td>
</tr>
<tr>
<td>Peak epicardial LD velocity</td>
<td>-1.53 ± 1.23</td>
<td>-1.73 ± 1.32</td>
<td>-2.60 ± 1.28</td>
<td>-4.23 ± 2.06</td>
</tr>
<tr>
<td>Peak LD MVG</td>
<td>-1.79 ± 0.95</td>
<td>-2.41 ± 1.13</td>
<td>-3.70 ± 1.18</td>
<td>-3.86 ± 1.31</td>
</tr>
<tr>
<td>Systole</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Peak endocardial S velocity</td>
<td>5.71 ± 1.19</td>
<td>5.49 ± 1.26</td>
<td>4.87 ± 1.42</td>
<td>5.03 ± 1.42</td>
</tr>
<tr>
<td>Peak mesocardial S velocity</td>
<td>4.73 ± 1.06</td>
<td>4.83 ± 1.29</td>
<td>4.45 ± 1.34</td>
<td>4.30 ± 1.13</td>
</tr>
<tr>
<td>Peak epicardial S velocity</td>
<td>3.32 ± 0.89</td>
<td>3.61 ± 1.05</td>
<td>3.35 ± 1.11</td>
<td>3.50 ± 1.23</td>
</tr>
<tr>
<td>Peak S MVG</td>
<td>4.61 ± 1.05</td>
<td>4.30 ± 1.49</td>
<td>3.50 ± 1.23</td>
<td>3.8 ± 1.82</td>
</tr>
</tbody>
</table>

Abbreviations: ED, early diastole; LD, late diastole; S, systole; MVG, myocardial velocity gradient. In the original table, “Early diastole” was referred to as “Protodiastole” and “Late diastole” as “Telediastole.” Results are expressed as mean ± standard deviation. Source: From Ref. 40.
consistent with predictions based on geometric constraints in a model of concentric cylinders, and are due to the incompressibility of the myocardium (44). In experimental models, the maximal rate of thinning of the total wall during early diastole was significantly greater than the maximal rate of thinning of the epicardial portion (45). It has been suggested that early diastolic mitral velocities reflect myocardial relaxation, which is an active, energy-consuming process (46). The nonuniform distribution of velocities during early diastole could be explained by a more active role played by the subendocardial and mesocardial layers in myocardial relaxation.

Table 2 (40) demonstrates that in all three myocardial layers, early diastolic mitral velocity decreases significantly with age. However, the impact of age on peak subendocardial velocity is greater than on the other more external myocardial layers (40). The relationship between age and relaxation of the normal myocardium is well known. Studies in isolated muscle preparations have demonstrated prolonged relaxation in aged rats (47). A progressive prolongation of myocardial relaxation also occurs in the human heart with normal aging (48). Furthermore, experimental studies in aging animals by Anversa and coworkers have demonstrated that progressive myocardial cell loss and replacement fibrosis take place mainly in the subendocardium of the LV (49). Thus, a wider extent of damage in the subendocardium with aging could explain a greater loss of its relaxation capability compared with the mesocardial and epicardial layers.

Late diastolic peak velocities increase progressively and similarly with age in all of the myocardial layers (40). It is postulated that the different behavior of age-related changes in late diastole compared to early diastole is related to the physiologic differences existing between these two periods. Specifically, late diastolic mitral velocities seem to be more related to atrial contraction than to an active phenomenon (such as relaxation) in the LV (50). For this reason, age-related changes in the subendocardium, which could be critical in early diastole, do not appear to be as relevant in late diastole. Of interest, increasing age does not appear to have a significant effect on systolic velocity in any of the three myocardial layers (Table 2).

Yamada and associates (51) also found a moderate inverse correlation between age and early diastolic myocardial velocity recorded in both the mid-ventricular septum and mid-LV posterior wall myocardium (range of \( r = -0.51 \) to \(-0.61 \), all \( p \) values < 0.0001). This finding was true whether the myocardial velocities were recorded from the long or short axis view. In contrast, Yamada et al. found that late diastolic (peak atrial systolic) velocities along both long and short axes correlated directly with age (range of \( r = 0.53 \) to \(0.65 \), all \( p < 0.0001 \)).

Of interest, Onose and associates (52) reported that the peak velocity of the first systolic wave in the LV posterior wall, recorded by tissue Doppler from the long-axis direction (in the apical long-axis view), correlated inversely with age (\( p < 0.0001 \)), but did not correlate significantly with the first derivative of the LV pressure (dP/dt) recorded at cardiac catheterization. The authors concluded that these results suggest that shortening of the longitudinal myocardial fibers in early systole is impaired with increased age in healthy individuals. They further postulated that this impairment results in insufficient spherical shape change in the LV cavity, although global LV pump function and myocardial contractility are apparently maintained (52). Similarly, in 118 healthy individuals (age range, 20–90 years), Nikitin et al. (53) used transmitial pulsed Doppler and color-coded myocardial tissue Doppler to assess LV relaxation and longitudinal LV function. These investigators also noted that systolic and early diastolic peak mitral annular velocities decreased (\( p < 0.0001 \)), while late diastolic (atrial) myocardial velocity increased (\( p = 0.0002 \)) in older compared to younger subjects. (Table 3) (53). The authors concluded that although global LV systolic function is preserved with age, the velocity of
long-axis systolic myocardial shortening is depressed in older individuals, indicating a selective impairment of the longitudinal component of systolic contraction.

Atrial mechanical function was assessed directly by Doppler tissue imaging in 131 healthy control subjects by Zhang et al. (54) These workers used echocardiography with color-coded tissue Doppler imaging to study the left atrial and right atrial free wall and intra-atrial septum, and found that peak atrial contraction velocity in the left atrium was higher in participants aged 60 years and older than in those who were younger than 60 years (8.1 ± 2.7 cm/sec vs. 6.7 ± 1.4 cm/sec, \( p < 0.001 \)). Similarly, the velocity in the right atrium was increased in the older (9.6 ± 2.8 cm/sec) compared to the younger age group (8.0 ± 2.1 cm/sec, \( p < 0.01 \)). In this study, both older age and faster heart rates were associated with increased peak atrial contraction velocity (54).

Strain/Strain Rate

Compared to measurements of tissue Doppler velocities, strain and strain rate measurements provide a purer assessment of contraction and relaxation because they tend to adjust for the components of the velocity vector due to translation and rotation of the heart, and they are less affected by tethering to adjacent myocardial segments. Strain rate is calculated as: \( \frac{V_A - V_B}{L} \), where \( V_A \) and \( V_B \) are the velocity of point A and B in the myocardium, and L is the myocardial distance between points A and B (55). To avoid the noise inherent in any differentiation method, strain rate data may be integrated throughout systole to obtain strain, a dimensionless measure of the total deformation that the myocardium undergoes during contraction. Strain is calculated as \( \frac{L - L_0}{L_0} \), where \( L_0 \) is the original (diastolic) length of the myocardium, and L is the length at end systole. When recorded by tissue Doppler from the apex, normal myocardium demonstrates negative strain during systole and positive strain during diastole.

Using tissue Doppler techniques, Sun et al. studied strain and strain rate, in addition to myocardial velocity, in 100 healthy volunteers (56). Measurements were obtained from basal, mid, and apical segments of the visualized left ventricle from the apical four-chamber and two-chamber views. Figure 19 shows the relationship of mean tissue Doppler velocity and strain rate parameters during systole and early and late diastole to age (56). Of note, all measured parameters showed a strong dependence on wall segment position (i.e., basal vs. mid vs. apical). Age dependence was less prominent for peak systolic tissue velocity and strain rate than it was for early and late diastolic tissue velocities and strain rates. Early diastolic velocity and strain rate decreased with age, whereas late diastolic velocity and strain rate increased with age (range of \( p \), 0.01 to

---

**Table 3** Systolic and Early and Late Diastolic Mitral Annular Velocities in Older Age Subgroups

<table>
<thead>
<tr>
<th>Age Subgroup</th>
<th>60–69 yr (n = 22)</th>
<th>70–79 yr (n = 23)</th>
<th>≥80 yr (n = 16)</th>
</tr>
</thead>
<tbody>
<tr>
<td>( S_m ) (cm/sec)</td>
<td>5.44 ± 1.06*</td>
<td>5.28 ± 1.11***</td>
<td>4.15 ± 0.79</td>
</tr>
<tr>
<td>( E_m ) (cm/sec)</td>
<td>5.49 ± 1.60***</td>
<td>4.45 ± 1.39***</td>
<td>3.09 ± 1.1</td>
</tr>
<tr>
<td>( A_m ) (cm/sec)</td>
<td>6.68 ± 1.15</td>
<td>7.12 ± 1.18***</td>
<td>6.04 ± 1.48</td>
</tr>
<tr>
<td>( E_m/A_m ) ratio</td>
<td>0.84 ± 0.26***</td>
<td>0.64 ± 0.20</td>
<td>0.53 ± 0.25</td>
</tr>
</tbody>
</table>

*\( p < 0.05 \) between groups 1 and 2, ***\( p < 0.05 \) between groups 2 and 3.

**Abbreviations:** \( S_m \), peak systolic mitral annular velocity; \( E_m \), peak early diastolic mitral annular velocity; \( A_m \), peak late diastolic annular velocity. **Source:** From Ref. 53.
Although myocardial velocities and strain rate showed a significant association with age, peak systolic strain measures appeared to be less age related.

Hees et al. (57) used magnetic resonance imaging and pulsed echo Doppler assessments of myocardial tissue velocities to determine whether the reduction in early diastolic filling in older adults is more closely related to reduced early diastolic left atrial pressure (loading) or to slower LV pressure decline. The authors found (Fig. 20) that older age was associated with a reduced ratio of early diastolic transmitral velocity to LV inflow velocity ($V_p$) ($p = 0.008$), a reduced ratio of early diastolic transmitral velocity—to early diastolic myocardial tissue velocity ($E/E_m$) ($p < 0.0001$), increased pulmonary venous systolic fraction ($p < 0.001$), and increased pulmonary venous deceleration time ($p = 0.0026$) (57). These findings all suggest reduced early diastolic left atrial pressure. Therefore, the authors concluded that reduced early LV filling in older adults may be more closely related to reduced early diastolic left atrial pressure than to slower LV pressure decline. These findings would also help explain the prolonged early diastolic LV relaxation time seen with increasing age.

Figure 19  Age dependence of mean Doppler tissue velocity and SR parameters. To obtain mean Doppler tissue velocity and SR parameters, individual segmental data were averaged over each individual. Age dependence was less prominent for peak systolic tissue velocity ($S'$) and SR (Panels A and B) than for early ($E'$) and late ($A'$) diastolic tissue velocities and SR (Panels C to F). Furthermore, regression coefficients were lower for SR compared with velocity data. Abbreviation: SR, strain rate. Source: From Ref. 56.
EPIDEMIOLOGICAL STUDIES IN THE ELDERLY

On the basis of M-mode echocardiography, the Framingham study showed that (1) LV hypertrophy is a powerful, independent predictor for mortality and morbidity from CHD, and (2) increased left atrial dimension is associated with an increased risk of stroke (58–60).

The Cardiovascular Health Study (CHS) is a multiyear prospective epidemiological study of 5201 men and women older than 65 years recruited from four U.S. field centers: Davis, California; Hagerstown, Maryland; Winston-Salem, North Carolina; and Pittsburgh, Pennsylvania (61). Echocardiography was performed to determine whether echocardiographic measurements, or changes in these measurements, are (1) correlated with traditional risk factors for CHD and stroke, and (2) independent predictors of morbidity and mortality from CHD and stroke.

Echocardiographic measurements obtained in CHS included those related to global and segmental LV systolic and diastolic structure and function and left atrial and aortic root dimension (62). For each subject, a baseline two-dimensional (2-D), M-mode (2-D directed), and Doppler ECG was recorded using a standard protocol. Images were digitized and measurements were made using customized computer algorithms. M-mode measurements were made according to American Society of Echocardiography conventions (63), and LV mass was calculated from the formula reported by Devereux et al.

\[
\text{LV mass (g)} = 0.80 \times 1.04\left[(\text{VST}_d + \text{LVID}_d + \text{PWT}_d)^{3} - (\text{LVID}_d)^{3}\right] + 0.6,
\]

Figure 20 Four indexes sensitive to changes in left atrial pressure, PV systolic fraction (top left), deceleration time (bottom left), E/E_m (top right) and E/V_p (bottom right), all vary with age (p < 0.0001, p = 0.0026, p = 0.0001, and p = 0.008, respectively). Abbreviation: PV, pulmonary vein. Source: From Ref. 57.
where VST\textsubscript{d} is ventricular septal thickness at end diastole, LVID\textsubscript{d} is LV internal dimension at end diastole, and PWT\textsubscript{d} is LV posterior wall thickness at end diastole (64).

Quality control measures included standardized training of echocardiography technicians and readers, technician observation by a trained echocardiographer, periodic blind duplicate readings with reader review sessions, phantom studies, and quality control audits (62).

**LV MASS**

M-mode measurements (2-D directed) of LV mass could not be made in 34% of CHS participants, and this was highly related to age (29% in the 65- to 69-year age group vs. 50% in the 85 or older age group; \( p < 0.001 \)), white race, male gender, and history of hypertension, diabetes, or CHD. LV mass was found to be significantly higher in men than women, even after multivariate adjustments, and increased modestly with aging (65,66). LV mass increased less than 1 g/yr in both men and women. Of interest, across all CHS age subgroups, the difference in weight-adjusted LV mass by sex was greater in magnitude than the difference related to clinical CHD (Fig. 21). This fact may relate to the relatively high prevalence of subclinical markers of CHD in elderly individuals without clinical disease.

After adjustment for traditional CVD risk factors, baseline LV mass was related to six- to seven-year incidence of CHD, congestive heart failure (CHF), and stroke among CHS participants initially free of prevalent disease (67). The highest quartile of LV mass conferred a hazard ratio of 3.36 for incident CHF compared with the lowest quartile. Further, eccentric and concentric LV hypertrophy conferred increased hazard ratios compared with normal LV geometry for both incident CHF (2.95 and 3.32, respectively) and CHD (2.05 and 1.61, respectively). In comparison, in a four-year follow-up of the original Framingham cohort (mean age 69 years), even higher relative risks (7.8 in men and 3.4 in women) for CHD events were found in the highest versus the lowest quartile of risk factor-adjusted LV mass (59).

![Figure 21](image-url)  
*Figure 21*  Bar graph showing weight-adjusted mean LV mass displayed by sex and disease status across 5-year age intervals. Data are computed using the lower age end point and the mean weight for each age category (65 to 69, 70 to 74, 75 to 79, 80 to 84, 85+ years). Weight-adjusted LV mass was significantly associated with sex, disease status, and age. Within each age group, the magnitude of the sex effect exceeded that of the disease effect (e.g., clinical CHD). *Abbreviations:* LV, left ventricular; CHD, coronary heart disease; HTN, hypertensive.
LV WALL MOTION

In CHS, 4.3% of participants with hypertension but no clinical heart disease and 1.9% of participants with neither clinical heart disease nor hypertension had LV segmental wall motion abnormalities, suggesting silent CHD (66). Multivariate analysis revealed male sex and presence of clinical CHD (both \( p < 0.001 \)) to be independent predictors of LV akinesis or dyskinesis.

SUBCLINICAL DISEASE

Assessments for subclinical CVD at the baseline CHS examination included measures of the ankle–brachial blood pressure index, carotid artery wall thickness and stenosis, ECG and echocardiographic abnormalities, and the Rose Angina and Claudication Questionnaire (Table 4) (68). Participants were followed for an average of 2.4 years (maximum 3 years). For participants without evidence of clinical CVD at baseline, the presence of subclinical disease compared with no subclinical disease was associated with a significantly increased risk of incident CHD in both men and women, including CHD death, nonfatal myocardial infarction, and angina pectoris. For individuals with subclinical disease, the relative risk for incident CHD was 2.0 for men and 2.5 for women, while the relative risk for total mortality was 2.9 for men and 1.7 for women. These increased risks were relatively unchanged after adjustment for other risk factors, including lipoprotein levels, blood pressure, smoking, and diabetes. Consequently, the measurement of subclinical disease provides an approach for identifying high-risk older individuals who may be candidates for more active intervention to prevent clinical disease.

Table 4 Criteria for Clinical and Subclinical Disease in the Cardiovascular Health Study

<table>
<thead>
<tr>
<th>Clinical disease criteria</th>
<th>Subclinical disease criteria</th>
</tr>
</thead>
<tbody>
<tr>
<td>Atrial fibrillation or pacemaker</td>
<td>Ankle-arm index &lt;0.9 mmHg</td>
</tr>
<tr>
<td>History of intermittent claudication or peripheral vascular surgery</td>
<td>Internal carotid wall thickness &gt;80th percentile</td>
</tr>
<tr>
<td>History of congestive heart failure</td>
<td>Common carotid wall thickness &gt;80th percentile</td>
</tr>
<tr>
<td>History of stroke, transient ischemic attack, or carotid surgery</td>
<td>Carotid stenosis &gt;25%</td>
</tr>
<tr>
<td>History of coronary artery bypass graft surgery or percutaneous transluminal coronary angioplasty</td>
<td>Major ECG abnormalitiesa</td>
</tr>
<tr>
<td>History of angina or use of nitroglycerin</td>
<td>Abnormal ejection fraction on echocardiogram</td>
</tr>
<tr>
<td>History of myocardial infarction</td>
<td>Abnormal wall motion on echocardiogram</td>
</tr>
<tr>
<td></td>
<td>Rose questionnaire claudication positive</td>
</tr>
<tr>
<td></td>
<td>Rose questionnaire angina positive</td>
</tr>
</tbody>
</table>

aData According to Minnesota Code, ventricular conduction defects (7–1, 7–2, 7–4); major Q/QS wave abnormalities (1–1, 1–2); left ventricular hypertrophy (high-amplitude R waves with major or minor ST–T abnormalities) (3–1, 3–3, and 4–1 to 4–3 or 5–1 to 5–3); isolated major ST/T wave abnormalities (4–1, 4–2, 5–1, 5–2). Source: From Ref. 37.
**“HEALTHY” SUBGROUP**

An apparently “healthy” subgroup of CHS participants was defined by excluding subjects with clinical heart disease, hypertension, reduced LV ejection fraction, or echocardiographic wall motion abnormalities. The healthy subgroup consisted of 516 men and 773 women, with 339 and 569, respectively, having available echo measurements of LV mass. Preliminary analysis indicated that after adjustment for weight, no adjustment for height was necessary. Likewise, after adjustment for weight, age had only a modest effect on LV mass. Therefore, for simplicity, the reference equations were not expressed as a function of age. There was no evidence of an interaction between sex and weight. Since race was not an independent predictor of LV mass in the original CHS cohort, the reference equations are not race specific.

The expected LV mass (g) derived from the CHS healthy subgroup can be calculated from the following equations:

Men : $16.6 \times \text{weight (kg)}^{0.51}$

Women : $13.9 \times \text{weight (kg)}^{0.51}$

If the ratio of observed to expected LV mass is between 0.69 and 1.47, the patient’s LV mass should be considered within the expected range for his or her weight. On the basis of these equations, 28% of the men and 18% of the women with clinical CHD were found to be outside the range of expected LV mass measurements. Exclusions of obese ($n = 220$) participants from the healthy group had a negligible effect on the reference equations.

**LV DIASTOLIC FILLING**

Pulsed Doppler transmitral flow velocities were analyzed as part of the baseline examination in the CHS (62). Early diastolic LV Doppler (transmitral) peak filling velocity decreased, and peak late diastolic (atrial) velocity increased with age in multivariate analyses (all $p < 0.001$) (69). Early and late diastolic peak filling velocities were both significantly higher in women than in men, even after adjustment for BSA (or height and weight). In multivariate models in the entire cohort and in a healthy subgroup ($n = 703$), gender, age, heart rate, and blood pressure were most strongly related to early and late diastolic transmitral peak velocities. Higher systolic blood pressure and lower diastolic blood pressure were associated with increased early and late diastolic peak velocities ($p < 0.001$). These increased early and late diastolic transmitral peak velocities may reflect increased central aortic stiffness. Doppler transmitral velocities were compared among health status subgroups. In multiple regression models adjusted for other covariates, and in analysis-of-variance models examining differences across subgroups adjusted only for age, the subgroup with CHF had the highest early diastolic peak velocities (69). All clinical disease subgroups had higher late diastolic peak velocities than did the healthy subgroup, with the CHF and hypertensive subgroups having the highest age-adjusted means. The hypertensive subgroup had the lowest ratio of early to late diastolic peak velocity, and men with CHF had the highest ratio. Borderline and definite isolated systolic hypertensions were positively associated with LV mass ($p < 0.001$), as well as with increases in transmitral late peak flow velocity and decreases in the ratio of early to late diastolic peak flow velocity (70). These findings are consistent with previous reports that hypertensive subjects exhibit an abnormal relaxation pattern, whereas CHF patients develop a pattern suggestive of an increased early diastolic LA-LV pressure gradient.
In summary, echocardiographic imaging and Doppler flow recordings have provided compelling evidence of structural and functional cardiac changes related to aging. In turn, these changes provide important insights into the cardiovascular epidemiology of aging (e.g., mechanisms underlying the increasing prevalence of diastolic HF and atrial fibrillation with advancing age). In addition, these techniques provide a framework for the clinical evaluation of elderly patients with suspected CVD.

ACKNOWLEDGMENT

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REFERENCES


Elderly Patients Without Clinical Heart Disease


INTRODUCTION

As in any body tissue or organ, changes take place in the cardiovascular system as life progresses. Some of these changes allow easy identification of the very elderly heart when examining autopsy cardiac specimens as unknowns. The “normal” elderly heart has relatively small ventricular cavities and relatively large atria and great arteries. The ascending aorta and left atrium, in comparison with the relatively small left ventricular cavity, appear particularly large. The coronary arteries increase in both length and width; the former, particularly in association with the decreasing size of the cardiac ventricles, results in arterial tortuosity. (The young river is straight and the old one winding.) The leaflets of each of the four cardiac valves thicken with age, particularly the atrioventricular valves; these have a smaller area to occupy in the ventricles because of the diminished size of the latter. Histological examination discloses large quantities of lipofuscin pigment in myocardial cells; some contain mucoid deposits (mucoid degeneration). These changes appear to affect all population groups of elderly individuals regardless of where they reside on the earth or their level of serum lipids. An elevated systemic arterial pressure appears to both accelerate and amplify these normal expected cardiac changes of aging. Both the aorta and its branches and the major pulmonary arteries and their branches enlarge with age. Because the enlargement is in both the longitudinal and the transverse dimension, the aorta, like the coronary arteries, tends to become tortuous. This process is further amplified as the vertebral bodies become smaller and the height becomes somewhat shorter. The major pulmonary arteries appear to be too short and have too low a pressure to dilate longitudinally.

The amount of information at necropsy in very elderly persons is relatively sparse. In 1983, Waller and Roberts (1) described some clinical and necropsy findings in 40 American patients aged 90 years and older. In 1988, Lie and Hammond (2) reported findings at necropsy in 237 patients aged 90 years and older. In 1991, Gertz and associates (3) described composition of coronary atherosclerotic plaques in 18 persons aged 90 years and older. In 1993, Roberts (4) described cardiac necropsy findings in an additional
53 patients aged 90 years and older. In 1995, Shirani et al. (5) described cardiac findings at necropsy in 366 Americans aged 80 to 89 years, and in 1998, Roberts (6) described cardiac findings at necropsy in six centenarians. Also, in 1998, Roberts and Shirani (7) compared cardiovascular findings in 490 patients studied at necropsy in the three age categories: 80–89; 90–99, and ≥100 years. This chapter expands on that previous comparative study.

METHODS

Patients

The files of the Pathology branch, National Heart, Lung, and Blood Institutes, National Institutes of Health, Bethesda, Maryland, from 1959 to 1993, and those of the Baylor University Medical Center, Dallas, Texas, beginning January 1993, were searched for all accessioned cases of patients aged 80 years and older. Of 511 such cases found, adequate clinical information was available in 490 necropsy patients, and they are the subject of this chapter. The clinical and cardiac morphological records, photographs, and postmortem radiographs, histological slides, and the initial gross description of the heart were reviewed. All 490 hearts were originally examined by WCR, who recorded gross morphological abnormalities in each case.

Sources of Patients

Of the 490 cases, the hearts in 412 were obtained from 12 Washington, D.C., area hospitals, and the hearts in the other 78 cases, from hospitals outside that area, including 25 from Baylor University Medical Center. Of the 490 hearts, 37 (8%) were examined in 1970 or before, 153 (31%) from 1971 through 1980, 244 (50%) from 1981 through 1990, and 56 (11%) from 1991 through 1997.

Definitions

Sudden coronary death was defined as death within six hours from the onset of new symptoms of myocardial ischemia in the presence of morphological evidence of significant atherosclerotic coronary artery disease (≥1 major epicardial coronary artery narrowed >75% in cross-sectional area by atherosclerotic plaque). Most patients who died suddenly did so outside a hospital; a few, however, died shortly after admission to an emergency room. Sudden, out-of-hospital death also occurred in some patients with cardiac disease other than atherosclerotic coronary artery disease. In each case, an underlying cardiac disease generally accepted to cause sudden death was present at necropsy. Acute myocardial infarction was defined as a grossly visible left ventricular wall lesion confirmed histologically to represent coagulation-type myocardial necrosis. Ischemic cardiomyopathy was defined as chronic congestive heart failure associated with a transmural healed myocardial infarct and a dilated left ventricular cavity.

Cardiac Morphological Data

Hearts were fixed in 10% phosphate-buffered formalin for 3 to 15 days before examination. They were “cleaned” of parietal pericardium and postmortem intracavity clot, and the pulmonary trunk and ascending aorta were incised approximately 2 cm
Morphological Features of the Elderly Heart

cephalad to the sinotubular junction. Heart weight was then measured on accurate scales by WCR (Lipsaw scale before 1971, accurate to 10 g, and Mettler P1210 scale after 1971, accurate to 0.1 g). Heart weight was considered increased if it was ≥350 g in women and >400 g in men. Most hearts were studied by cutting the ventricles transversely at approximately 1-cm-thick intervals from apex to base parallel to the atrioventricular groove posteriorly. In each heart, the sizes of cardiac ventricular cavities (determined by gross inspection), presence of left ventricular necrosis (acute myocardial infarct) and fibrosis (healed myocardial infarct), status of the four cardiac valves, and the maximal degree of cross-sectional luminal narrowing in each of the three major (left anterior descending, left circumflex, and right) epicardial coronary arteries were recorded.

RESULTS

Number of Patients in Each of the Three Groups

Certain clinical and necropsy cardiac findings in the 490 cases are summarized in Table 1 and illustrated in Figures 1 through 19. The 490 patients were divided into three groups: the octogenarians (80–89 years) \([n = 391 (80\%)]\), the nonagenarians (90–99 years) \([n = 93 (19\%)]\), and the centenarians (≥100 years) \([n = 6 (1\%)]\).

Table 1 Certain Clinical and Necropsy Findings in 490 Patients Aged 80–103 Years

<table>
<thead>
<tr>
<th>Variables</th>
<th>Age group (yr)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>80–89 ((n = 391))</td>
</tr>
<tr>
<td>1. Mean age (yr)</td>
<td>84 ± 4</td>
</tr>
<tr>
<td>2. Male:female</td>
<td>194 (50%):97 (50%)</td>
</tr>
<tr>
<td>3. Angina pectoris</td>
<td>137 (35%)</td>
</tr>
<tr>
<td>4. Acute myocardial infarction</td>
<td>78 (20%)</td>
</tr>
<tr>
<td>5. Chronic congestive heart failure</td>
<td>140 (36%)</td>
</tr>
<tr>
<td>6. Systemic hypertension (history)</td>
<td>174 (44%)</td>
</tr>
<tr>
<td>7. Diabetes mellitus</td>
<td>56 (14%)</td>
</tr>
<tr>
<td>8. Atrial fibrillation</td>
<td>57 (15%)</td>
</tr>
<tr>
<td>9. Heart weight (g): range (mean)</td>
<td>185–900 (449)</td>
</tr>
<tr>
<td>Women</td>
<td>185–900 (409)</td>
</tr>
<tr>
<td>10. Cardiomegaly</td>
<td></td>
</tr>
<tr>
<td>Men &gt; 400 g</td>
<td>103/154 (67%)</td>
</tr>
<tr>
<td>Women &gt; 350 g</td>
<td>133/165 (81%)</td>
</tr>
<tr>
<td>11. Cardiac calcific deposits</td>
<td></td>
</tr>
<tr>
<td>None</td>
<td>43 (11%)</td>
</tr>
<tr>
<td>Present</td>
<td>348 (89%)</td>
</tr>
<tr>
<td>Coronary arteries</td>
<td>304 (78%)</td>
</tr>
<tr>
<td>Aortic valve cusps</td>
<td>164 (42%)</td>
</tr>
<tr>
<td>Heavy (stenosis)</td>
<td>43 (11%)</td>
</tr>
<tr>
<td>Mitral annulus</td>
<td>146 (37%)</td>
</tr>
<tr>
<td>Heavy</td>
<td>52 (13%)</td>
</tr>
<tr>
<td>Papillary muscle</td>
<td>37 (9%)</td>
</tr>
</tbody>
</table>

(Continued)
Table 1  Certain Clinical and Necropsy Findings in 490 Patients Aged 80–103 Years (Continued)

<table>
<thead>
<tr>
<th>Variable</th>
<th>80–89 (n = 391)</th>
<th>90–99 (n = 93)</th>
<th>≥100 (n = 6)</th>
</tr>
</thead>
<tbody>
<tr>
<td>12. Number of patients with 0, 1, 2, or 3 major (right, left anterior descending, left circumflex) coronary arteries ↓ &gt;75% in cross-sectional area</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0</td>
<td>159 (41%)</td>
<td>33 (35%)</td>
<td>2</td>
</tr>
<tr>
<td>1</td>
<td>67 (59%)</td>
<td>20 (65%)</td>
<td>2</td>
</tr>
<tr>
<td>2</td>
<td>71 232 (59%)</td>
<td>32 60 (65%)</td>
<td>2 4</td>
</tr>
<tr>
<td>3</td>
<td>94 (59%)</td>
<td>8 (65%)</td>
<td>0</td>
</tr>
<tr>
<td>Mean</td>
<td>1.7</td>
<td>1.5</td>
<td>1.5</td>
</tr>
<tr>
<td>13. Number of major coronary arteries (3/patient) ↓ &gt;75% in cross-sectional area by plaque</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0</td>
<td>0/477</td>
<td>0/99</td>
<td>0/6</td>
</tr>
<tr>
<td>1</td>
<td>67/201</td>
<td>20/60</td>
<td>2/6</td>
</tr>
<tr>
<td>2</td>
<td>142/213</td>
<td>64/96</td>
<td>4/6</td>
</tr>
<tr>
<td>3</td>
<td>282/282</td>
<td>24/24</td>
<td>0</td>
</tr>
<tr>
<td>Total</td>
<td>491/1173 (42%)</td>
<td>108/279 (39%)</td>
<td>6/18 (33%)</td>
</tr>
<tr>
<td>14. Left ventricular necrosis and/or fibrosis</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Necrosis only</td>
<td>54/(14%)</td>
<td>10 (11%)</td>
<td>0</td>
</tr>
<tr>
<td>Fibrosis only</td>
<td>101 (26%)</td>
<td>20 (21%)</td>
<td>2</td>
</tr>
<tr>
<td>Both</td>
<td>37 (9%)</td>
<td>5 (5%)</td>
<td>0</td>
</tr>
<tr>
<td>15. Ventricular cavity dilatation</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Neither</td>
<td>222 (57%)</td>
<td>58 (62%)</td>
<td>4</td>
</tr>
<tr>
<td>One</td>
<td>84 (21%)</td>
<td>4 (4%)</td>
<td>2</td>
</tr>
<tr>
<td>Right ventricle</td>
<td>42</td>
<td>2</td>
<td>2</td>
</tr>
<tr>
<td>Left ventricle</td>
<td>42</td>
<td>2</td>
<td>2</td>
</tr>
<tr>
<td>Both</td>
<td>85 (22%)</td>
<td>31 (34%)</td>
<td>0</td>
</tr>
<tr>
<td>16. Cardiac amyloidosis (massive)</td>
<td>14 (4%)</td>
<td>8 (9%)</td>
<td>0</td>
</tr>
</tbody>
</table>

Of the 490 cases, 248 (51%) were women and 242 (49%) were men.

**CLINICAL FINDINGS**

The clinical manifestations of the various cardiac disorders probably represent minimal numbers: many patients, apparently, were unable to provide much clinical information, many came to the hospital from nursing homes, and many had varying degrees of dementia. Nevertheless, angina pectoris was noted in the records of 137 (35%) of the 391 octogenarians, in 5 (5%) of the 93 nonagenarians, and in none of the centenarians. A history of hospitalization for an illness compatible with acute myocardial infarction was present in 78 (20%) of the 391 octogenarians, in 18 (19%) of the 93 nonagenarians, and in none of the six octogenarians. Chronic congestive heart failure was present in 36% (140/391) of the octogenarians, in 25% (23/93) of the nonagenarians, and in none of the six centenarians. A history of systemic hypertension was present in 45% (174/391) of the octogenarians, in 54% (50/93) of the nonagenarians, and in none of the centenarians.
Figure 1  Tortuous and heavily calcified coronary arteries in a 95-year-old woman (SH #A80–74) who never had symptoms of cardiac dysfunction and who died from a perforated gastric ulcer. (Top left): Postmortem radiogram of the excised R, LM, LAD, and LC coronary arteries. (Top center): Radiogram of a portion of the heart after removing the walls of the atria and most of the walls of the ventricles. (Top right and lower panels): Photomicrographs of coronary arteries at sites of maximal narrowing by calcified atherosclerotic plaques. (Movat stains; magnification: 17×, reduced 40%). This case illustrates extensive calcific deposits in the coronary arteries without significant luminal narrowing. Abbreviations: R, right; LM, left main; LAD, left anterior descending; LC, left circumflex; MVA, mitral valve annulus.
Diabetes mellitus was present in 14% (56/391) of the octogenarians, in 9% (8/93) of the nonagenarians, and in none of the centenarians.

**CAUSES OF DEATH**

The causes of death in the 490 patients are summarized in Table 2. A cardiac condition was the cause of death in 51% (198/391) of the octogenarians, in 30% (30/99) of the nonagenarians, and in none of the centenarians. A noncardiac but vascular condition was
Morphological Features of the Elderly Heart

Table 2  Causes of Death in the 490 Necropsy Patients Aged 80–103 Years

<table>
<thead>
<tr>
<th>Age group (yr)</th>
<th>80–89 (n = 391)</th>
<th>90–99 (n = 93)</th>
<th>≥100 (n = 6)</th>
</tr>
</thead>
<tbody>
<tr>
<td>I. Cardiac</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>A. Coronary artery disease</td>
<td>198 (51%)</td>
<td>30 (32%)</td>
<td>0</td>
</tr>
<tr>
<td>1. Acute myocardial infarction</td>
<td>129/198 (65%)</td>
<td>12/30 (40%)</td>
<td>0</td>
</tr>
<tr>
<td>2. Chronic congestive heart failure</td>
<td>90</td>
<td>12</td>
<td>0</td>
</tr>
<tr>
<td>3. Sudden</td>
<td>15</td>
<td>3</td>
<td>0</td>
</tr>
<tr>
<td>4. Coronary bypass</td>
<td>7</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>B. Valvular heart disease</td>
<td>41/198 (21%)</td>
<td>3/30 (10%)</td>
<td>0</td>
</tr>
<tr>
<td>1. Aortic stenosis</td>
<td>33</td>
<td>3</td>
<td>0</td>
</tr>
<tr>
<td>2. Aortic regurgitation</td>
<td>2</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>3. Mitral regurgitation</td>
<td>5</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>4. Mitral stenosis</td>
<td>1</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>C. Primary cardiomyopathy</td>
<td>7/198 (4%)</td>
<td>1/30 (3%)</td>
<td>0</td>
</tr>
<tr>
<td>1. Hypertrophic</td>
<td>4</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>2. Idiopathic dilated</td>
<td>3</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>D. Secondary cardiomyopathy</td>
<td>16/198 (8%)</td>
<td>8/30 (27%)</td>
<td>0</td>
</tr>
<tr>
<td>1. Amyloidosis</td>
<td>14</td>
<td>8</td>
<td>0</td>
</tr>
<tr>
<td>2. Hemosiderosis</td>
<td>1</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>3. Myocarditis</td>
<td>1</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>E. Pericardial heart disease</td>
<td>3/198 (2%)</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>II. Vascular, noncardiac</td>
<td>52 (13%)</td>
<td>19 (20%)</td>
<td>0</td>
</tr>
<tr>
<td>A. Stroke</td>
<td>17/52 (33%)</td>
<td>6/19 (32%)</td>
<td>0</td>
</tr>
<tr>
<td>B. Abdominal aortic aneurysm</td>
<td>14/52 (33%)</td>
<td>5/19 (26%)</td>
<td>0</td>
</tr>
<tr>
<td>C. Peripheral arterial disease</td>
<td>11/52 (21%)</td>
<td>5/19 (26%)</td>
<td>0</td>
</tr>
<tr>
<td>D. Aortic dissection</td>
<td>4/52 (8%)</td>
<td>0/19 (0)</td>
<td>0</td>
</tr>
<tr>
<td>E. Pulmonary embolism</td>
<td>6*/52 (11%)</td>
<td>3/19* (16%)</td>
<td>0</td>
</tr>
<tr>
<td>III. Noncardiac, nonvascular</td>
<td>141 (36%)</td>
<td>44 (47%)</td>
<td>6 (100%)</td>
</tr>
<tr>
<td>A. Cancer</td>
<td>52/141 (37%)</td>
<td>13/44 (29%)</td>
<td>0/6</td>
</tr>
<tr>
<td>B. Infection</td>
<td>37/141 (26%)</td>
<td>17/44 (39%)</td>
<td>0/6</td>
</tr>
<tr>
<td>C. Fall complication</td>
<td>10/141 (7%)</td>
<td>3/44 (7%)</td>
<td>3/6</td>
</tr>
<tr>
<td>D. Other</td>
<td>42/141 (30%)</td>
<td>11/44 (25%)</td>
<td>3/6</td>
</tr>
</tbody>
</table>

All had underlying chronic obstructive pulmonary disease.

Cardiac necropsy findings at necropsy are tabulated in Table 1.

Heart Weight

The mean heart weights were largest in the octogenarians and smallest in the centenarians (449 g vs. 420 g vs. 328 g). Heart weight was increased (>400 g in men; >350 g in women) in 131 (64%) of the 205 men and in 157 (74%) of the women, and the percentage was highest in the octogenarians.
Figure 3 Heart and coronary arteries in a 93-year-old woman who was hospitalized with worsening chronic congestive heart failure. (Top left): Postmortem radiogram showing calcific deposits in the R, LAD, and LC coronary arteries and in the MVA and aortic valve. (Top right): View of RV and LV and VS showing a transmural scar (arrows). (Bottom): Coronary arteries at sites of maximal narrowing. (Movat stains; magnification: 17×, reduced 40%). Abbreviations: R, right; LAD, left anterior descending; LC, left circumflex; MVA, mitral valve annulus; RV, right ventricle; LV, left ventricle; VS, ventricular septum; LM, left main.

Figure 4 This 91-year-old woman (LRC #3) had a “typical” clinical acute myocardial infarct, which was fatal. (Left): Postmortem radiogram showing calcific deposits in the R, LM, LAD, and LC coronary arteries. (Right): View of the left and right (RV) ventricles showing transmural necrosis and fibrosis (arrows) and dilated ventricles. Abbreviations: R, right; LM, left main; LAD, left anterior descending; LC, left circumflex; VS, ventricular septum.
Calcific Deposits in the Heart

Calcific deposits were present in the heart at necropsy in 444 (91%) of the 490 patients and were most common in the coronary arteries in 81% (398/490)—in all cases being located in atherosclerotic plaques and not in the media; in the aortic valve cusps in 47% (228/490)—heavy enough to result in aortic stenosis in 10% (51/490); mitral valve annulus in 39% (190/490)—very heavy deposits in 13% (63/490), and in the apices of one or both left ventricular papillary muscles in 17% (85/490). The cardiac calcific deposits were more frequent and heavier in the nonagenarians than in the octogenarians.

Numbers of Patients with Narrowing of One or More Major Epicardial Coronary Arteries

Among the 490 patients, 194 (40%) had none of the three major (right, left anterior descending, and left circumflex) epicardial coronary arteries narrowed by plaque >75% in cross-sectional area; 89 (18%) had one artery so narrowed; 105 (21%) had two arteries so narrowed; and 94 (19%) had all three arteries so narrowed. The percentage of patients in each of the three groups with no arteries and one, two, and three arteries narrowed >75% was similar.
This 97-year-old man (GT # 69A-585) had complete heart block and had a pacemaker inserted when he was 91 years old. (Left): Radiogram of heart at necropsy showing calcific deposits in the LAD, LC, and R coronary arteries and a pacemaker wire in the RV. (Right): Electrocardiogram. Abbreviations: LAD, left anterior descending; LC, left circumflex; R, right; RV, right ventricle; L, left ventricle.
Number of Major Coronary Arteries (Three/Patient) Narrowed >75% in Cross-Sectional Area by Plaque

Among the 490 patients, a total of 1470 major epicardial coronary arteries were examined: 865 (59%) arteries had insignificant (<75% in cross-sectional area) narrowing and 605 (41%) had narrowing by plaque >75% in cross-sectional area. The percentage of arteries significantly narrowed was similar in each of the three groups (42% vs. 39% vs. 33%).

Acute and Healed Myocardial Infarcts

Grossly visible foci of left ventricular wall (includes ventricular septum) necrosis (acute infarcts) without associated left ventricular scars (healed infarcts) were found in 64 (13%) patients, foci of left ventricular fibrosis without associated necrosis were observed in 123 patients (25%), and foci of both necrosis and fibrosis were found in 42 patients (9%). Thus, a total of 229 (47%) of the 490 patients had grossly visible evidence of acute or healed myocardial infarcts or both. The percentages of patients with myocardial lesions of ischemia were similar among the octogenarians and nonagenarians.

Ventricular Cavity Dilatation

One or both ventricular cavities were dilated (by gross inspection) in 218 (44%) of the 490 patients and no significant differences were observed in the three groups.
Cardiac Amyloidosis

Grossly visible amyloid (confirmed histologically) in ventricular and atrial myocardium as well as in atrial mural endocardium was present in 22 patients (4%). In these 22 patients, the amyloidosis was symptomatic and fatal. A number of other patients who had no gross evidence of cardiac amyloidosis had small foci in the heart on histological study. These minute deposits did not cause symptoms of cardiac dysfunction. In the 22 patients with fatal cardiac amyloidosis, deposits of amyloid also were present in several other body organs at necropsy.

ELECTROCARDIOGRAPHIC FINDINGS

Information on electrocardiograms was available on 30 of the 99 patients aged 90 years and older. Of the 30 patients, three had electrocardiograms recorded during acute myocardial infarction. The electrocardiograms in all three, however, disclosed only atrial fibrillation and complete left bundle branch block, and these findings in these patients
were known to be present before the fatal acute myocardial infarction. The electrocardiograms in the other 27 patients were not recorded during periods of acute myocardial infarction. Of the 30 patients on whom electrocardiographic information was available, 8 had clinical evidence of heart disease and 22 did not; the findings are summarized in Table 2. The total 12-lead QRS voltage ranged from 82 to 251 mm (mean 151; 10 mm = 1 mV). In the 19 women, the total voltage ranged from 82 to 251 mm (mean 158) and, in the 5 men, from 105 to 154 mm (mean 101; p < 0.05). The total 12-lead QRS voltage did not correlate with either heart or body weight. The 24 patients in whom the total 12-lead QRS voltage was measured were separated into two groups: 8 patients in whom clinical evidence of cardiac dysfunction was present (coronary heart disease in five, massive cardiac amyloid in two, and aortic valve stenosis in one) and 16 patients without such evidence. Comparison of the total QRS voltage in the 8 patients with and in the 16 patients without clinical evidence of heart disease disclosed no significant difference (mean 147 mm vs. 152 mm). Breakdown on the eight patients with cardiac dysfunction did show some differences: the total 12-lead QRS voltage in the five patients with angina pectoris or acute myocardial infarction ranged from 123 to 163 mm (mean 143); in the two patients with massive cardiac amyloidosis it was 102 and 117 mm (mean 109), and in the one patient with aortic valve stenosis it was 238 mm. Of the 29 patients on whom

**Figure 9** Mean percentage cross-sectional area narrowing by atherosclerotic plaques in 1789 segments (5 mm) of the four major epicardial coronary arteries in 36 necropsy patients aged 90 years and older, 10 of whom had angina pectoris or acute myocardial infarction, or both, and 26 of whom did not. The mean percentage of narrowing for each 5-mm segment differs significantly in the group with clinical evidence of myocardial ischemia (55%) and the group without such evidence.
information was available, 18 (62%) received digitalis and only two appeared to have evidence of digitalis toxicity.

**COMMENTS**

This study describes findings in a large group \((n = 490)\) of patients aged 80 years and older studied at necropsy, and it compares certain clinical and necropsy findings in the octogenarians, nonagenarians, and centenarians. Despite study of nearly 500 patients, only 6 (1%) lived 100 years or longer, and only 93 (19%) lived into the tenth decade of life. Nevertheless, the ratio of one centenarian for every 65 octogenarians is much higher than expected. In general, it takes 10,000 persons to reach age 85 before one reaches age 100 (8).

Another finding was the high frequency of men: 248 men (51%) and 242 women (49%). A higher than expected percentage of men may have resulted in part from receiving a number of these cases from a Veterans Administration Hospital and from a retirement home filled almost entirely by men.
The causes of death were divided into three major types: cardiac = 228/490 (47%), vascular but noncardiac = 71/490 (14%), and noncardiac and nonvascular = 191/490 (39%). The frequency of a cardiac condition causing death decreased with increasing age groups (51% vs. 32% vs. 0), and the frequency of a noncardiac and nonvascular condition causing death increased with increasing age groups (36% vs. 47% vs. 100%). Among the cardiac conditions, coronary artery disease was the problem in 62% (141/228) of the patients, and the other cardiac conditions, mainly aortic valve stenosis [36/228(16%)] and cardiac amyloidosis [22/228(10%)], in the other 38%. Stroke, rupture of an abdominal aortic aneurysm, and complications of peripheral arterial atherosclerosis were the major
vascular (noncardiac) conditions causing death. Of the noncardiac and nonvascular causes of death, cancer and infection, mainly pneumonia, were the major conditions, 35% (65/185) and 29% (54/185), respectively, among the octogenarians and nonagenarians.

The cardiac necropsy findings focused primarily on calcific deposits in the coronary arteries, aortic valve cusps, and mitral valve annulus and their consequences, and, to a lesser extent, on heavy amyloid deposits in the heart. Calcific deposits were present in the atherosclerotic plaques of one or more epicardial coronary arteries in 81% (398/490) of the patients, on the aortic aspects of the aortic valve cusps in 47% (228/490), in the mitral annular region in 39% (190/490), and in one or both left ventricular papillary in 25% (122/490). The calcific deposits tended to be less frequent in the octogenarians. The frequent presence of calcific deposits in the coronary arteries, aortic valve cusps, and mitral annular region in the same patient suggests that the cause of the calcific deposits in each of these three locations is the same. The calcific deposits in the coronary arteries indicate the presence of atherosclerosis because calcium occurs in the coronary arteries, with one exception (9), only in the plaques and not in the media. It is reasonable to believe that the calcific deposits in and on the aortic cusps, at least when this valve is tricuspid, are another manifestation of atherosclerosis. Because mitral annular calcium in this older population is nearly always associated with calcium in the coronary arteries, it is also reasonable to believe that mitral annular calcium in persons aged 80 years and older also is a manifestation of atherosclerosis. Calcium in a papillary muscle appears to be a consequence of aging and not a direct manifestation of atherosclerosis.

When the deposits of calcium on the aortic aspects of the aortic valve cusps are extensive, the cusps may become relatively or absolutely immobile, resulting in aortic

Figure 12 (A) A 90-year-old woman (GT #80A126) with heavy mitral valve annular calcific deposits that reduced the mitral valve orifice to <1 cm in diameter. The unusual feature of the mitral calcium in this patient was that it was not only located behind the posterior mitral leaflet (mitral annular region) but it also extended across the anterior mitral leaflet, nearly producing a letter O, as has been described previously. She died from rupture of a descending thoracic aortic aneurysm. (B) View of the left ventricle at the level of the tips of the mitral leaflets, showing a very small cavity. Abbreviation: VS, ventricular septum.
Figure 13  A 97-year-old woman (SH #A81–62) who never had clinical evidence of cardiac dysfunction and who died from cancer. (A) External view of anterior surface of the heart showing an increased amount of subepicardial fat. (B) Postmortem radiogram showing calcific deposits in the MVA and AV. (C) Radiogram of the excised coronary arteries showing a few calcific deposits. (D) View of AV and PV from above. (E) View of left ventricle showing calcific deposits (arrows) in the papillary muscles. (F) Calcific deposits in the mitral annular region (arrows). Abbreviations: Ao, aorta; LV, left ventricle; PT, pulmonary trunk; RV, right ventricle; LA, left atrium; RA, right atrium; LAD, left anterior descending; LC, left circumflex; LM, left main; R, right; MVA, mitral valve annulus; AV, aortic valve; PV, pulmonic valve.
valve stenosis. These valves usually lack commissural fusion (i.e., adherence of two cusps together near the lateral attachments) and, therefore, aortic regurgitation is usually absent. Although it is most often associated with some degree of mitral regurgitation, mitral annular calcium may result in mitral stenosis, provided the mitral annular calcium is “massive” and the left ventricular cavity is small and the wall quite thickened (10).

Although the calcific deposits in the epicardial coronary arteries were located entirely in atherosclerotic plaques, which are located in the intima, the presence of calcific deposits in the coronary arteries in this older population did not necessarily indicate the presence of significant (>75% cross-sectional area) luminal narrowing. In contrast, the presence of calcific deposits in epicardial coronary arteries in persons aged less than 65 years generally indicates the presence of significant luminal narrowing. The calcific deposits tended to occur in each of the four major (right, left main, left anterior descending, and left circumflex) epicardial arteries and were always larger in the proximal than in the distal halves of the right, left anterior descending, and left circumflex arteries or, if small, limited to their proximal halves. The plaques consisted mainly (87% ± 8%) of fibrous tissue with calcific deposits forming 7% ± 6% of the plaques (3). The percentage of patients with narrowing >75% in cross-sectional area by plaque of one or more major epicardial coronary arteries was similar in all the three age groups, as was the percentage of major coronary arteries narrowed significantly.

In 36 patients (all ≥90 years of age), each of the four major coronary arteries were divided into 5-mm-long segments and the degree of cross-sectional area narrowing by atherosclerotic plaque was determined for each segment. Of the 1789 5-mm segments in the 36 patients, the average amount of cross-sectional area narrowing by atherosclerotic plaques per segment was 42% (range, 19–69). Of the 467 5-mm segments in the 10 patients with clinical evidence of coronary artery disease, the average amount of cross-sectional area narrowing per segment was 55% (range, 43–69), and of the 1322 5-mm segments in the 26 patients without clinical evidence of coronary artery disease, it was 38% (range, 19–40; p < 0.01). Among 129 patients aged 22 to 85 years (mean 56), the amount of cross-sectional area narrowing by atherosclerotic plaques per segment averaged 67%; in the control subjects, that is, those without symptomatic coronary artery
Figure 15  A 95-year-old man (SH #79–77) who never had symptoms of cardiac dysfunction and died from sarcoma. The coronary arteries are shown in Figure 2. (Left): Radiogram of heart at necropsy showing considerable enlargement of the aorta in comparison to the ventricles. (Right): Aortic valve from above. The coronary arteries were excised before the radiogram and photographs were taken. Abbreviations: LV, left ventricle; RV, right ventricle; R, right; L, left; P, posterior sinuses of Valsalva.
disease, cross-sectional area narrowing averaged 32%. The mean percentage of 5-mm coronary segments narrowed by 76–100% in cross-sectional area in the 36 patients was 13% (range, 2–89); of the 10 patients with symptomatic coronary artery disease, the mean was 19% (range, 10–34); and of the 26 patients without symptomatic coronary artery disease, the mean was 7% (range, 2–28) ($p < 0.05$). The mean of 19% in patients with symptomatic coronary artery disease aged 90 years and older was half of that observed in patients younger than 85 years (mean 56) with fatal coronary artery disease, and the mean of 7% was nearly three times that observed in the younger patients without fatal coronary artery disease (11).

**Figure 16** A 90-year-old man (DCGH #69A391) with chronic, eventually fatal, congestive heart failure from clinically unrecognized cardiac amyloidosis. (A) External view of the heart showing prominent LV and LAA. (B) Right-to-left longitudinal cut of the heart (four-chamber, two-dimensional echocardiographic view) showing thickened ventricular walls and dilated RA and LA. (C) Photomicrograph of a portion of the left ventricle showing extensive amyloid deposits. (D) Photomicrograph of LA wall showing amyloid deposits in endocardium (E) and in myocardium (M). (Hematoxylin and eosin; magnification: 100× (C) and 25× (D), both reduced by 35%).

**Abbreviations:** LV, left ventricle; LAA, left atrial appendage; RA, right atrium; LA, left atrium; PT, pulmonary trunk; RAA, right atrial appendage; RV, right ventricle; VS, ventricular septum.
Figure 17  Electrocardiograms in four patients, each recorded at age 90 years or older. None ever had symptoms of cardiac dysfunction, and each died from noncardiac conditions. (Top left): The electrocardiogram was recorded 43 days before death (A66–13) and showed a normal heart (weight 270 g). (Top right): The electrocardiogram was recorded 11 days before death (GT #68A325) and showed left QRS axis deviation and a slightly prolonged PR interval (heart weight 400 g). (Bottom left): This electrocardiogram was recorded 28 days before death (A64–62) and showed left axis deviation and complete left bundle branch block (heart weight 320 g). (Bottom right): This electrocardiogram was recorded 128 days before death (SH #A80–74) and showed atrial fibrillation, left axis deviation, and complete right bundle branch block (heart weight 440 g).
These detailed morphological studies of the coronary arteries in these very elderly persons suggest that the degree of severe coronary narrowing necessary to have a fatal or nearly fatal coronary event is considerably less than that necessary to have a coronary event in younger patients. Moreover, these studies indicate that these very elderly patients without symptoms of coronary artery disease have distinctly more coronary luminal narrowing by atherosclerotic plaque than control subjects who are younger (mean age, 52 years) (11). The latter observation suggests that coronary artery disease may be underdiagnosed clinically in the very elderly.

Clinical diagnosis of cardiac and other conditions in patients aged 80 years and over, particularly those aged 90 years and older, appears more difficult than in younger persons. Historical information may be difficult to obtain because of impaired intellect on the part of the patient and an impaired diagnostic pursuit on the part of the physician. Physicians caring for these very elderly persons may focus primarily on the prevention of suffering and only secondarily on accurate diagnosis or longer-term therapy. Patients aged 90 years and over generally have outlived their spouses and private physicians and are often “inherited” by nursing home physicians, who may have limited access to earlier medical records.

Angina pectoris appears particularly difficult to diagnose in the very elderly because they may not be able to describe this symptom. Acute myocardial infarction is

Figure 18 Various QRS complexes, and how each was measured. Source: From Siegel RJ, Roberts WC. Electrocardiograph observations in severe aortic valve stenosis: correlative necropsy study of clinical, hemodynamic, and ECG variables demonstrating relation of 12-lead QRS amplitude to peak systolic transaortic pressure gradient. Am Heart J 1982; 103:210-221.
also difficult to diagnose clinically, but it is often fatal in the very elderly. Furthermore, the electrocardiogram is not as useful in diagnosis of acute myocardial infarction in the very elderly because left bundle branch block is frequent and, of course, it prevents the appearance of typical changes. Serial recordings of electrocardiograms also appear to be quite infrequent in the very elderly.

Physical examination in the very elderly may be both difficult and misleading. The lack of mobility may prevent proper positioning of the elderly patient for proper examining. Precordial murmurs, although common, infrequently indicate significant functional abnormality. Although calcific deposits in the aortic valve are common, actual aortic valve stenosis is not nearly as frequent. Likewise, although mitral annular calcific deposits are common, these calcific deposits rarely narrow the mitral orifice or produce significant mitral regurgitation.

Electrocardiographic abnormalities are common in elderly persons. Of my patients for whom electrocardiograms were available, all had one or more abnormalities recorded, the most frequent being abnormal axis, atrial fibrillation, and complete bundle branch block. Although 15 of the 30 patients had cardiomegaly (>350 g in women; >400 g in men) at necropsy, only one had voltage criteria for left ventricular hypertrophy. Likewise, only one had low voltage. Measurement of the QRS amplitude in each of the 12 leads was performed in 24 patients. The total QRS voltage was similar in the eight patients with and

**Figure 19** Cardiac changes in the very elderly. The LA cavity enlarges, and the LV cavity becomes smaller. The amount of space available for the mitral leaflets decreases with aging, and consequently the number of scallops in the leaflets appears to increase. *Abbreviations:* LA, left atrium; LV, left ventricle. *Source:* From Roberts WC, Perloff JK. Mitral valvular disease. A clinicopathologic survey of the conditions causing the mitral valve to function abnormally. Ann Intern Med 1972; 77:939–975.
in the 16 patients without clinical evidence of cardiac disease (mean 147 vs. 152 mm; 10 mm = 1 mV).

SUMMARY

Certain clinical and necropsy cardiac findings are described and compared in 391 octogenarians (80%), 93 nonagenarians (19%), and 6 centenarians (1%). The numbers of men and women were similar [248(51%)] and [242(49%)]. The cause of death was cardiac in 228 patients (47%), vascular but noncardiac in 71 (14%), and noncardiac and nonvascular in 191 (39%). The frequency of a cardiac condition causing death decreased with increasing age groups (51% vs. 32% vs. 0), and the frequency of a noncardiac, nonvascular condition causing death increased with increasing age groups (36% vs. 47% vs. 100%). Among the cardiac conditions causing death, coronary artery disease was the problem in 61% (141/228) followed by aortic valve stenosis in 16% (36/228) and cardiac amyloidosis in 10% (22/228). Calcific deposits were found at necropsy in the coronary arteries in 81% (398/490) of the patients, in the aortic valve in 47% (228/490), in the mitral annular area in 39% (190/490), and in one or both left ventricular papillary muscles in 25% (122/490). The calcific deposits tended to be less frequent in the octogenarians. Three hundred (61%) of the 490 patients had one or more major coronary arteries narrowed by more than 75% in cross-sectional area by plaque, and the percentage of patients in each of the three age groups was similar to the percentage of coronary arteries significantly narrowed in them.

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Cardiovascular Drug Therapy in the Elderly

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Cardiovascular disease is the greatest cause of morbidity and mortality in the elderly, and cardiovascular drugs are the most widely prescribed drugs in this population. Since many cardiovascular drugs have narrow therapeutic windows in the elderly, the incidence of adverse effects from using these drugs is also highest in the elderly. The appropriate use of cardiovascular drugs in the elderly requires knowledge of age-related physiologic changes, the effects of concomitant diseases that alter the pharmacokinetic and pharmacodynamic effects of cardiovascular drugs, and drug interactions.

PHARMACOKINETIC CONSIDERATIONS IN THE ELDERLY

Absorption
Age-related physiologic changes, which may affect absorption, include reduced gastric secretion of acid, decreased gastric emptying rate, reduced splanchnic blood flow, and decreased mucosal absorptive surface area (Table 1). Despite these physiologic changes, the oral absorption of cardiovascular drugs is not significantly affected by aging, probably because most drugs are absorbed passively (1).

Bioavailability
There are almost no data available for age-related changes in drug bioavailability for routes of administration other than the oral route (2). The bioavailability of cardiovascular drugs depends on the extent of drug absorption and on first-pass metabolism by the liver and/or the
wall of the gastrointestinal (GI) tract. In the elderly, the absolute bioavailability of drugs such as propranolol, verapamil, and labetalol is increased because of reduced first-pass hepatic extraction (3). However, the absolute bioavailability of prazosin in the elderly is reduced (4).

### Drug Distribution

With aging there is a reduction in lean body mass (5) and in total body water (6), causing a decrease in volume of distribution ($V_d$) of hydrophilic drugs. This decrease leads to higher plasma concentrations of hydrophilic drugs such as digoxin and angiotensin converting enzyme (ACE) inhibitors with the first dose in the elderly (7). The increased proportion of body fat that occurs with aging also causes an increased $V_d$ for lipophilic drugs. This leads to lower initial plasma concentrations for lipophilic drugs such as most $\beta$ blockers, antihypertensive drugs, and central $\alpha$ agonists.

The level of $\alpha_1$-acid glycoprotein increases in the elderly (8). Weak bases, such as disopyramide, lidocaine, and propranolol, bind to $\alpha_1$-acid glycoprotein. This may cause a reduction in the free fraction of these drugs in the circulation, a decreased $V_d$, and a higher initial plasma concentration (9). In the elderly, there is also a tendency for plasma albumin concentration to be reduced (10). Weak acids, such as salicylates and warfarin, bind extensively to albumin. Decreased binding of drugs such as warfarin to plasma albumin may result in increased free-drug concentrations, resulting in more intense drug effects (11).

### Table 1

<table>
<thead>
<tr>
<th>Process</th>
<th>Physiologic change</th>
<th>Result</th>
<th>Drugs affected</th>
</tr>
</thead>
<tbody>
<tr>
<td>Absorption</td>
<td>Reduced gastric acid production</td>
<td>Reduced tablet dissolution and decreased solubility of basic drugs</td>
<td>$\downarrow \beta$ blockers, central $\alpha$ agonists</td>
</tr>
<tr>
<td></td>
<td>Reduced gastric emptying rate</td>
<td>Decreased absorption for acidic drugs</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Reduced GI mobility, GI blood flow, absorptive surface</td>
<td>Less opportunity for drug absorption</td>
<td></td>
</tr>
<tr>
<td>Distribution</td>
<td>Decreased total body mass. Increased proportion of body fat</td>
<td>Increased $V_d$ of highly lipid-soluble drugs</td>
<td>$\uparrow$ digoxin &amp; ACE inhibitors</td>
</tr>
<tr>
<td></td>
<td>Decreased proportion of body water</td>
<td>Decreased $V_d$ of hydrophilic drugs</td>
<td>$\uparrow$ disopyramide and warfarin, lidocaine, propranolol</td>
</tr>
<tr>
<td></td>
<td>Decreased plasma albumin, disease-related</td>
<td>Changed % of free drug, $V_d$, and measured levels of bound drugs</td>
<td></td>
</tr>
<tr>
<td></td>
<td>increased $\alpha_1$-acid glycoprotein, altered relative tissue perfusion</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Metabolism</td>
<td>Reduced liver mass, liver blood flow, and hepatic metabolic capacity</td>
<td>Accumulation of metabolized drugs</td>
<td>$\uparrow$ propranolol, nitrates, lidocaine, diltiazem, warfarin, labetalol, verapamil, mexiletine digoxin, ACE inhibitors, antiarrhythmic drugs, atenolol, sotalol, nadolol</td>
</tr>
<tr>
<td>Excretion</td>
<td>Reduced glomerular filtration, renal tubular function, and renal blood flow</td>
<td>Accumulation of renally cleared drugs</td>
<td></td>
</tr>
</tbody>
</table>

Abbreviations: GI, gastrointestinal; ACE, angiotensin-converting enzyme.

Source: From Ref. 181.
Half-Life

The half-life of a drug (or of its major metabolite) is the length of time in hours that it takes for the serum concentration of that drug to decrease to half of its peak level. This definition can be described by the kinetic equation: \( t_{1/2} = \frac{0.693}{V_d/Cl} \), where \( t_{1/2} \) is directly related to drug distribution and inversely to clearance (Cl). Therefore, changes in \( V_d \) and/or Cl due to aging, as previously mentioned, can affect the half-life of a drug. In elderly patients, an increased half-life of a drug means a longer time until steady-state conditions are achieved. With a prolonged half-life of a drug, there may be an initial delay in maximum effects of the drug and prolonged adverse effects. Table 2 lists the pharmacokinetic changes, routes of elimination, and dosage adjustment for common cardiovascular drugs used in the elderly.

**Table 2** Pharmacokinetic Changes, Route of Elimination, and Dosage Adjustment of Selected Cardiovascular Drugs in the Elderly

<table>
<thead>
<tr>
<th>Drug</th>
<th>( t_{1/2} )</th>
<th>( V_d )</th>
<th>Cl</th>
<th>Primary route(s) of elimination</th>
<th>Dosage adjustment</th>
</tr>
</thead>
<tbody>
<tr>
<td>( \alpha )-Adrenergic agonists (centrally acting)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Clonidine</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>Hepatic/renal</td>
<td>Initiate at lowest dose; titrate to response</td>
</tr>
<tr>
<td>Guanabenz</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>Hepatic</td>
<td>Initiate at lowest dose; titrate to response</td>
</tr>
<tr>
<td>Guanfacine</td>
<td>↑</td>
<td>–</td>
<td>↓</td>
<td>Hepatic/renal</td>
<td>Initiate at lowest dose; titrate to response</td>
</tr>
<tr>
<td>Methyldopa</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>Hepatic</td>
<td>Initiate at lowest dose; titrate to response</td>
</tr>
<tr>
<td>( \alpha_1 )-selective adrenergic antagonists (peripherally acting)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Doxazosin</td>
<td>↑</td>
<td>↑</td>
<td>↑a</td>
<td>Hepatic</td>
<td>Initiate at lowest dose; titrate to response</td>
</tr>
<tr>
<td>Prazosin</td>
<td>↑</td>
<td>–</td>
<td>–</td>
<td>Hepatic</td>
<td>Initiate at lowest dose; titrate to response</td>
</tr>
<tr>
<td>Terazosin</td>
<td>↑</td>
<td>–</td>
<td>–</td>
<td>Hepatic</td>
<td>Initiate at lowest dose; titrate to response</td>
</tr>
<tr>
<td>Angiotensin-converting enzyme inhibitors</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Benazepril</td>
<td>↑</td>
<td>–</td>
<td>↓</td>
<td>Renal</td>
<td>No adjustment needed</td>
</tr>
<tr>
<td>Captopril</td>
<td>NS</td>
<td>–</td>
<td>↓</td>
<td>Renal</td>
<td>Initiate at lowest dose; titrate to response</td>
</tr>
<tr>
<td>Enalapril</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>Renal</td>
<td>Initiate at lowest dose; titrate to response</td>
</tr>
<tr>
<td>Fosinopril</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>Hepatic/renal</td>
<td>No adjustment needed</td>
</tr>
<tr>
<td>Lisinopril</td>
<td>↑</td>
<td>NS</td>
<td>↓</td>
<td>Renal</td>
<td>Initiate at lowest dose; titrate to response</td>
</tr>
<tr>
<td>Moexipril</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>Hepatic/renal</td>
<td>Initiate at lowest dose; titrate to response</td>
</tr>
<tr>
<td>Perindopril</td>
<td>–</td>
<td>–</td>
<td>↓</td>
<td>Renal</td>
<td>Initiate at lowest dose; titrate to response</td>
</tr>
<tr>
<td>Quinapril</td>
<td>–</td>
<td>–</td>
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<td>Renal</td>
<td>Initiate at lowest dose; titrate to response</td>
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<tr>
<td>Ramipril</td>
<td>–</td>
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</tr>
<tr>
<td>Trandolapril</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>Hepatic/renal</td>
<td>Initiate at lowest dose; titrate to response</td>
</tr>
</tbody>
</table>

(Continued)
### Table 2  Pharmacokinetic Changes, Route of Elimination, and Dosage Adjustment of Selected Cardiovascular Drugs in the Elderly (Continued)

<table>
<thead>
<tr>
<th>Drug</th>
<th>$t_\frac{1}{2}$</th>
<th>$V_d$</th>
<th>$Cl$</th>
<th>Primary route(s)</th>
<th>Dosage adjustment</th>
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<tbody>
<tr>
<td><strong>Angiotensin II receptor blockers</strong></td>
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<tr>
<td>Candesartan</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>Hepatic/renal</td>
<td>No adjustment needed</td>
</tr>
<tr>
<td>Eprosartan</td>
<td>–</td>
<td>–</td>
<td>↓</td>
<td>Hepatic/biliary/renal</td>
<td>No adjustment needed</td>
</tr>
<tr>
<td>Irbesartan</td>
<td>NS</td>
<td>–</td>
<td>–</td>
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<td>No adjustment needed</td>
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<tr>
<td>Losartan</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>Hepatic</td>
<td>No adjustment needed</td>
</tr>
<tr>
<td>Olmesartan</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>Renal/biliary</td>
<td>No adjustment needed</td>
</tr>
<tr>
<td>Telmisartan</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>Hepatic/biliary</td>
<td>No adjustment needed</td>
</tr>
<tr>
<td>Valsartan</td>
<td>↑</td>
<td>–</td>
<td>–</td>
<td>Hepatic</td>
<td>No adjustment needed</td>
</tr>
<tr>
<td><strong>Antiarrhythmic agents</strong></td>
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<td></td>
<td></td>
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<td><strong>Class I</strong></td>
<td></td>
<td></td>
<td></td>
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<td>Disopyramide</td>
<td>↑</td>
<td>–</td>
<td>↓</td>
<td>Renal</td>
<td>Initiate at lowest dose; titrate</td>
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<tr>
<td>Flecainide</td>
<td>↑</td>
<td>↑</td>
<td>↓</td>
<td>Hepatic/renal</td>
<td>to response</td>
</tr>
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<td>Lidocaine</td>
<td>↑</td>
<td>↑</td>
<td>NS</td>
<td>Hepatic</td>
<td>Initiate at lowest dose; titrate</td>
</tr>
<tr>
<td>Mexilitine</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>Hepatic</td>
<td>to response</td>
</tr>
<tr>
<td>Moricizine</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>Hepatic</td>
<td>No adjustment needed</td>
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<tr>
<td>Procainamide</td>
<td>–</td>
<td>–</td>
<td>↓</td>
<td>Renal</td>
<td>Initiate at lowest dose; titrate</td>
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<td>Propafenone</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>Hepatic</td>
<td>to response</td>
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<tr>
<td>Quinidine</td>
<td>↑</td>
<td>NS</td>
<td>↓</td>
<td>Hepatic</td>
<td>Initiate at lowest dose; titrate</td>
</tr>
<tr>
<td>Tocainide</td>
<td>↑</td>
<td>–</td>
<td>↓</td>
<td>Hepatic/renal</td>
<td>to response</td>
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<tr>
<td><strong>Class II (see β blockers)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td><strong>Class III</strong></td>
<td></td>
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<td>Amiodarone</td>
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<td>–</td>
<td>Hepatic/biliary</td>
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<td>Bretyllium</td>
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<td>–</td>
<td>–</td>
<td>Renal</td>
<td>Initiate at lowest dose; titrate</td>
</tr>
<tr>
<td>Dofetilide</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>Renal</td>
<td>to response</td>
</tr>
<tr>
<td>Ibutilide</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>Hepatic</td>
<td>No adjustment needed</td>
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<tr>
<td>Sotalol</td>
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<td>–</td>
<td>–</td>
<td>Renal</td>
<td>Adjust dose based on renal function</td>
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<tr>
<td><strong>Class IV (see calcium channel blockers)</strong></td>
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<td>Enoxaparin</td>
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<td>↓</td>
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(Continued)
Table 2  Pharmacokinetic Changes, Route of Elimination, and Dosage Adjustment of Selected Cardiovascular Drugs in the Elderly (Continued)

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<th>Drug</th>
<th>$t_{1/2}$</th>
<th>$V_d$</th>
<th>$Cl$</th>
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<td>Hepatic</td>
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<tr>
<td>$\beta_1$ selective with ISA</td>
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<td>$\downarrow$</td>
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(Continued)
### Table 2  Pharmacokinetic Changes, Route of Elimination, and Dosage Adjustment of Selected Cardiovascular Drugs in the Elderly (Continued)

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<th>Drug</th>
<th>$t_{1/2}$</th>
<th>$V_d$</th>
<th>$Cl$</th>
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<td>↓</td>
<td>Hepatic</td>
<td>Initiate at lowest dose; titrate to response</td>
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<td>Hepatic</td>
<td>Use usual dose with caution</td>
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<td>NS</td>
<td>↓</td>
<td>Hepatic</td>
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<td>NS</td>
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<td>Hepatic</td>
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<td>NS</td>
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<td>↓</td>
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(Continued)
### Pharmacokinetic Changes, Route of Elimination, and Dosage Adjustment of Selected Cardiovascular Drugs in the Elderly (Continued)

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<th>$Cl$</th>
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<td>Initiate at lowest dose; titrate to response</td>
</tr>
<tr>
<td>Epinephrine</td>
<td></td>
<td></td>
<td></td>
<td>Sympathetic nerve endings/plasma</td>
<td>Initiate at lowest dose; titrate to response</td>
</tr>
<tr>
<td>Isoproterenol</td>
<td></td>
<td></td>
<td></td>
<td>Renal</td>
<td>Initiate at lowest dose; titrate to response</td>
</tr>
<tr>
<td>Metaraminol</td>
<td></td>
<td></td>
<td></td>
<td>Hepatic/biliary/renal</td>
<td>Initiate at lowest dose; titrate to response</td>
</tr>
<tr>
<td>Methoxamine</td>
<td></td>
<td></td>
<td></td>
<td>Unknown</td>
<td>Initiate at lowest dose; titrate to response</td>
</tr>
<tr>
<td>Midodrine</td>
<td></td>
<td></td>
<td></td>
<td>Tissue/hepatic/renal</td>
<td>No initial adjustment needed</td>
</tr>
<tr>
<td>Milrinone</td>
<td></td>
<td></td>
<td></td>
<td>Renal</td>
<td>Adjust based on renal function</td>
</tr>
<tr>
<td>Norepinephrine</td>
<td></td>
<td></td>
<td></td>
<td>Sympathetic nerve endings/hepatic</td>
<td>Initiate at lowest dose; titrate to response</td>
</tr>
<tr>
<td>Phenylephrine</td>
<td></td>
<td></td>
<td></td>
<td>Hepatic/intestinal</td>
<td>Initiate at lowest dose; titrate to response</td>
</tr>
<tr>
<td>Vasopressin</td>
<td></td>
<td></td>
<td></td>
<td>Hepatic</td>
<td>Adjust dose based on hepatic function and response</td>
</tr>
<tr>
<td><strong>Lipid-lowering agents</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>BAS</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cholestyramine</td>
<td></td>
<td></td>
<td></td>
<td>Not absorbed in GI tract</td>
<td>No adjustment needed</td>
</tr>
<tr>
<td>Colestipol</td>
<td></td>
<td></td>
<td></td>
<td>Not absorbed in GI tract</td>
<td>No adjustment needed</td>
</tr>
</tbody>
</table>

(Continued)
<table>
<thead>
<tr>
<th>Drug</th>
<th>$t_{1/2}$</th>
<th>$V_d$</th>
<th>$Cl$</th>
<th>Primary route(s) of elimination</th>
<th>Dosage adjustment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Colesevelam</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>Not absorbed in GI tract</td>
<td>No adjustment needed</td>
</tr>
<tr>
<td>SCAI</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>Small intestine/hepatic/Biliary</td>
<td>No adjustment needed</td>
</tr>
<tr>
<td>Ezetimibe</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>Renal</td>
<td>Initiate at lowest dose; titrate to response</td>
</tr>
<tr>
<td>SCAI</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>Renal</td>
<td>No adjustment necessary</td>
</tr>
<tr>
<td>Fenofibrate</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>Hepatic/renal</td>
<td>Initiate at lowest dose; titrate to response</td>
</tr>
<tr>
<td>Gemfibrozil</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>Hepatic/renal</td>
<td>Initiate at lowest dose; titrate to response</td>
</tr>
<tr>
<td>Nicotinic acid</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>Hepatic/renal</td>
<td>Initiate at lowest dose; titrate to response</td>
</tr>
<tr>
<td>HMG CoA Reductase Inhibitors</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Atorvastatin</td>
<td>↑</td>
<td>–</td>
<td>–</td>
<td>Hepatic/biliary</td>
<td>No initial adjustment needed</td>
</tr>
<tr>
<td>Fluvastatin</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>Hepatic</td>
<td>No initial adjustment needed</td>
</tr>
<tr>
<td>Lovastatin</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>Hepatic/fecal</td>
<td>No initial adjustment needed</td>
</tr>
<tr>
<td>Pravastatin</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>Hepatic</td>
<td>No initial adjustment needed</td>
</tr>
<tr>
<td>Rosuvastatin</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>Hepatic/fecal</td>
<td>No initial adjustment needed</td>
</tr>
<tr>
<td>Simvastatin</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>Hepatic/fecal</td>
<td>Initiate at lowest dose; titrate to response</td>
</tr>
<tr>
<td>Neuronal and Ganglionic Blockers</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Guanadrel</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>Hepatic/renal</td>
<td>Initiate at lowest dose; titrate to response</td>
</tr>
<tr>
<td>Guanethidine</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>Hepatic/renal</td>
<td>Initiate at lowest dose; titrate to response</td>
</tr>
<tr>
<td>Mecamylamine</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>Renal</td>
<td>Initiate at lowest dose; titrate to response</td>
</tr>
<tr>
<td>Reserpine</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>Hepatic/fecal</td>
<td>Initiate at lowest dose; titrate to response</td>
</tr>
<tr>
<td>Vasodilators</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Alprostadil</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>Pulmonary/renal</td>
<td>Initiate at lowest dose; titrate to response</td>
</tr>
<tr>
<td>Cilostazol</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>Hepatic/renal</td>
<td>No adjustment necessary</td>
</tr>
<tr>
<td>Diazoxide</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>Hepatic/renal</td>
<td>Initiate at lowest dose; titrate to response</td>
</tr>
<tr>
<td>Epoprostenol</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>Hepatic/renal</td>
<td>Initiate at usual dose with caution</td>
</tr>
<tr>
<td>Fenoldopam</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>Hepatic</td>
<td>No adjustment necessary</td>
</tr>
<tr>
<td>Hydralazine</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>Hepatic</td>
<td>Initiate at lowest dose; titrate to response</td>
</tr>
<tr>
<td>ISDN</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>Hepatic</td>
<td>Initiate at lowest dose; titrate to response</td>
</tr>
<tr>
<td>ISMN</td>
<td>NS</td>
<td>NS</td>
<td>–</td>
<td>Hepatic</td>
<td>No adjustment necessary</td>
</tr>
<tr>
<td>Isoxsuprine</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>Renal</td>
<td>Initiate at lowest dose; titrate to response</td>
</tr>
<tr>
<td>Minoxidil</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>Hepatic</td>
<td>Initiate at lowest dose; titrate to response</td>
</tr>
<tr>
<td>Nitroglycerin</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>Hepatic</td>
<td>Initiate at lowest dose; titrate to response</td>
</tr>
<tr>
<td>Nitroprusside</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>Hepatic/renal/erythrocytes</td>
<td>Use usual dose with caution</td>
</tr>
</tbody>
</table>

(Continued)
Cardiovascular Drug Therapy in the Elderly

Table 2  Pharmacokinetic Changes, Route of Elimination, and Dosage Adjustment of Selected Cardiovascular Drugs in the Elderly (Continued)

<table>
<thead>
<tr>
<th>Drug</th>
<th>$t_{1/2}$</th>
<th>$V_d$</th>
<th>$Cl$</th>
<th>Primary route(s) of elimination</th>
<th>Dosage adjustment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Papaverine</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>Hepatic</td>
<td>Initiate at lowest dose; titrate to response</td>
</tr>
<tr>
<td>Pentoxifylline</td>
<td>–</td>
<td>–</td>
<td>↓</td>
<td>Hepatic/renal</td>
<td>Use usual dose with caution; dose reduction may be needed</td>
</tr>
<tr>
<td>Sildenafil</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>Hepatic/fecal</td>
<td>Initiate at lowest dose; titrate to response</td>
</tr>
</tbody>
</table>

*Increase in $Cl$ is small compared with increase in $V_d$.

Abbreviations: $t_{1/2}$, half-life; $V_d$, volume of distribution; $Cl$, clearance; ↑, increase; ↓, decrease; –, no information or not relevant; NS, no significant change; LMWH, low molecular weight heparin; ISA, intrinsic sympathomimetic activity; GI, gastrointestinal; BAS, bile acid sequestrants; SCAI, selective cholesterol absorption inhibitors; FADS, fibrin acid derivatives; HMG CoA, hydroxymethylglutaryl coenzyme A; ISDN, isosorbide dinitrate; ISMN, isosorbide mononitrate.

Source: From Ref. 182.

Drug Metabolism

Decreased hepatic blood flow, liver mass, liver volume, and hepatic metabolic capacity occur in the elderly (12). There is a reduction in the rate of many drug oxidation reactions (phase 1) and little change in drug conjugation reactions (phase 2). These changes in the elderly may result in higher serum concentrations of cardiovascular drugs that are metabolized in the liver, including propranolol, lidocaine, labetalol, verapamil, diltiazem, nitrates, warfarin, and mexiletine.

Drug Excretion

With aging there is a reduction in the total number of functioning nephrons and thereby a parallel decline in both glomerular filtration rate and renal plasma flow (13,14). The age-related decline in renal function is likely the single most important physiologic change causing pharmacokinetic alterations in the elderly. The change in renal function with aging is insidious and poorly characterized by serum creatinine determinations, although serum creatinine measurements remain one of the most widely used tests for gauging renal function. To estimate renal function from a serum creatinine value requires its being indexed for muscle mass, which is difficult in even the most skilled hands. Creatinine is a byproduct of creatine metabolism in muscle and its daily production correlates closely with muscle mass. Thus, the greater the muscle mass, the higher the “normal serum creatinine.” For example, in a heavily muscled male, a serum creatinine value of 1.4 mg/dL might be considered normal, though such a value may be considered grossly abnormal in an individual with less muscle, such as an aged individual. A safer way to estimate renal function in the elderly is by use of a urine-free formula, such as the Cockcroft–Gault formula (15):

$$\text{Creatinine clearance (mL/min)} = (140 - \text{age}) \times \text{body weight (kg)} / 72 \times S_{\text{creat}} (\text{mg/dL})$$

For females, the results of this equation can be multiplied by 0.85 to account for the small muscle mass in most females. It should be appreciated that creatinine clearance is reciprocally related to serum creatinine concentrations, such that a doubling of serum
creatinine represents an approximate halving of renal function. The axiom that glomerular filtration rate is reciprocally related to serum creatinine is most important with the first doubling of serum creatinine. For example, a serum creatinine value of 0.6 mg/dL in an elderly subject doubles to 1.2 mg/dL, and with this doubling creatinine clearance falls from 80 cc/min to about 40 cc/min.

The National Kidney Foundation guidelines use the Modification of Diet in Renal Disease (MDRD) equation to estimate the glomerular filtration rate (16). The MDRD equation is

$$\text{Glomerular filtration rate (mL/min/1.73m}^2\text{)} = 186 \times \frac{\text{S}_{\text{crea}}^{1.154} \times \text{age}^{-0.203} \times 0.742}{\text{if female} \times 1.210 \text{ if Black}}$$

The reduced clearance of many drugs primarily excreted by the kidneys causes their half-life to be increased in the elderly. Cardiovascular drugs known to be excreted by the kidney, via various degrees of filtration and tubular secretion, include digoxin, diuretics, ACE inhibitors, antiarrhythmic medications (breytilum, disopyramide, flecainide, procainamide, and tocinamide), and the β blockers (atenolol, bisoprolol, carteolol, nadolol, and sotalol). Typically, a renally cleared compound begins to accumulate when creatinine clearance values drop below 60 cc/min. An example of this phenomenon can be seen with ACE inhibitors (17) wherein accumulation begins early in the course of renal functional decline. Moreover, ACE inhibitor accumulation in the elderly is poorly studied in the case of many of the ACE inhibitors, particularly as relates to the “true level of renal function” when an otherwise healthy elderly subject undergoes formal pharmacokinetic testing. Thus, it has not been uncommon for elderly subjects with serum creatinine values as high as 2.0 mg/dL to be allowed entry into a study whose primary purpose is to determine the difference in drug handling of a renally cleared compound in young versus elderly subjects.

**PHARMACODYNAMICS**

There are numerous physiologic changes with aging that affect pharmacodynamics with alterations in end-organ responsiveness (Table 3). Increased peripheral vascular resistance is the cause of systolic and diastolic hypertension in the elderly (18). Inappropriate

<table>
<thead>
<tr>
<th>Physiologic changes</th>
<th>Changes in response</th>
</tr>
</thead>
<tbody>
<tr>
<td>Decreased cardiac reserve</td>
<td>Potential for heart failure</td>
</tr>
<tr>
<td>Decreased LV compliance due to thickened ventricular wall, increased blood viscosity, decreased aortic compliance, increased total and peripheral resistance</td>
<td>Decrease of cardiac output</td>
</tr>
<tr>
<td>Decreased baroreceptor sensitivity</td>
<td>Tendency to orthostatic hypotension</td>
</tr>
<tr>
<td>Diminished cardiac and vascular responsiveness to β agonists and antagonists</td>
<td>Decreased sensitivity to β agonists and antagonists</td>
</tr>
<tr>
<td>Suppressed renin-angiotensin-aldosterone system</td>
<td>Theoretically decreased response to ACE inhibitors, but not observed</td>
</tr>
<tr>
<td>Increased sensitivity to anticoagulant agents</td>
<td>Increased effects of warfarin</td>
</tr>
<tr>
<td>Concurrent illnesses</td>
<td>Increased drug-disease interactions</td>
</tr>
<tr>
<td>Multiple drugs</td>
<td>Increased drug-drug interactions</td>
</tr>
<tr>
<td>Sinus and AV node dysfunction</td>
<td>Potential for heart block</td>
</tr>
</tbody>
</table>

**Abbreviations:** LV, left ventricular; ACE, angiotensin-converting enzyme; AV, atrioventricular.

**Source:** From Ref. 181.
Cardiovascular Drug Therapy in the Elderly

sodium intake and retention may contribute to increased arteriolar resistance and/or plasma volume. Cardiac output, heart rate, renal blood flow, glomerular filtration rate, and renin levels decline with age. Increased arterial stiffness, resulting from changes in the arterial media and an increase in arterial tonus and arterial impedance, increases systolic blood pressure and contributes to a widened pulse pressure. Maintenance of α-adrenergic vasoconstriction with impaired β-adrenergic-mediated vasodilation may be an additional contributory factor to increased peripheral vascular resistance. The cardiovascular response to catecholamines and carotid arterial baroreflex sensitivity are both decreased in the elderly. Left ventricular (LV) mass and left atrial dimension are increased, and there is a reduction in both the LV early diastolic filling rate and volume (18).

The pharmacodynamic, chronotropic, and inotropic effects of β agonists and β blockers on β1-adrenergic receptors are diminished in the elderly (19–21). The density of β receptors in the heart is unchanged in the elderly, but there is a decrease in the ability of β-receptor agonists to stimulate cyclic adenosine monophosphate production (22). There are also age-related changes in the cardiac conduction system, as well as an increase in arrhythmias in the elderly. In the Framingham Study, the prevalence of atrial fibrillation was 1.8% in persons 60 to 69 years old, 4.8% in those 70 to 79 years old, and 8.8% in those 80 to 89 years old (23). In a study of 3624 elderly patients (mean age 81 years), the prevalence of atrial fibrillation was 16% (1160) in elderly men and 13% (2464) in elderly women (24).

In elderly patients with unexplained syncope, a 24-hour ambulatory electrocardiogram (ECG) should be obtained to rule out the presence of second-degree or third-degree atrioventricular block or sinus node dysfunction with pauses of more than 3 seconds not seen on the resting ECG. These phenomena were observed in 21 of 148 patients (14%) with unexplained syncope (25). These 21 patients included 8 with sinus arrest, 7 with advanced second-degree atrioventricular block, and 6 with atrial fibrillation with a slow ventricular rate that is not drug induced. Unrecognized sinus node or atrioventricular node dysfunction may become evident in elderly persons after drugs such as amiodarone, β blockers, digoxin, diltiazem, procainamide, quinidine, or verapamil are administered. Clinical use of these drugs in the elderly, therefore, must be carefully monitored.

USE OF CARDIOVASCULAR DRUGS IN THE ELDERLY

Digoxin

Digoxin has a narrow toxic-therapeutic ratio, especially in the elderly (26). Decreased renal function and lean body mass may increase serum digoxin levels in this population. Serum creatinine may be normal in elderly persons despite a marked reduction in creatinine clearance, thereby decreasing digoxin clearance and increasing serum digoxin levels. Older persons are also more likely to take drugs that interact with digoxin by interfering with bioavailability and/or elimination. Quinidine, cyclosporin, itraconazole, calcium preparations, verapamil, amiodarone, diltiazem, triamterene, spironolactone, tetracycline, erythromycin, propafenone, and propantheline can increase serum digoxin levels. Hypokalemia, hypomagnesemia, hypercalcaemia, hypoxia, acidosis, acute and chronic lung disease, hypothyroidism, and myocardial ischemia may also cause digitalis toxicity despite normal serum digoxin levels. Digoxin may also cause visual disturbances (27), depression, and confusional states in older persons, even with therapeutic blood levels.

Indications for using digoxin are slowing a rapid ventricular rate in patients with supraventricular tachyarrrhythmias such as atrial fibrillation, and treating patients with congestive heart failure (CHF) in sinus rhythm associated with abnormal LV ejection fraction that does not respond to diuretics, ACE inhibitors, and β blockers with a class IIa
indication (28). Digoxin should not be used to treat patients with CHF in sinus rhythm associated with normal LV ejection fraction. By increasing contractility through increasing intracellular calcium ion concentration, digoxin may increase LV stiffness and increase LV filling pressures, adversely affecting LV diastolic dysfunction. Since almost half the elderly patients with CHF have normal LV ejection fractions (29,30), the LV ejection fraction should be measured in all older patients with CHF so that appropriate therapy may be given (31). Many older patients with compensated CHF who are in sinus rhythm and are on digoxin may have the drug withdrawn without decompensation in cardiac function (32,33).

A post hoc subgroup analysis of data from women with an LV ejection fraction less than 45% in the Digitalis Investigator Group (DIG) study showed by multivariate analysis that digoxin significantly increased the risk of death among women by 23% (absolute increase of 4.2%) (34). A post hoc subgroup analysis of data from men with an LV ejection fraction less than 45% in the DIG study showed that digoxin significantly reduced mortality by 6% if the serum digoxin level was 0.5 to 0.8 ng/mL, insignificantly increased mortality by 3% if the serum digoxin level was 0.8 to 1.1 ng/mL, and significantly increased mortality by 12% if the serum digoxin level was greater than 1.2 ng/mL (35).

Another post hoc subgroup analysis of data from all 1926 women with systolic or diastolic HF in the DIG study showed that digoxin significantly increased mortality by 20% in women (36). However, digoxin did not increase mortality in women with an LV ejection fraction less than 35% and a serum digoxin level of 0.5 to 1.1 ng/mL (37). In women with an LV ejection fraction less than 35% and a serum digoxin level greater than 1.2 ng/mL, digoxin significantly increased mortality 1.83 times (37).

Therapeutic levels of digoxin do not reduce the frequency or duration of episodes of paroxysmal atrial fibrillation detected by 24-hour ambulatory ECGs (38). In addition, therapeutic concentrations of digoxin do not prevent the occurrence of a rapid ventricular rate in patients with paroxysmal atrial fibrillation (38,39). Many elderly patients are able to tolerate atrial fibrillation without the need for digoxin therapy because the ventricular rate is slow as a result of concomitant atrioventricular nodal disease.

Some studies have suggested that digoxin may decrease survival after acute myocardial infarction (MI) in patients with LV dysfunction (40,41). Leor et al. (42) showed that digoxin may exert a dose-dependent deleterious effect on survival in patients after acute MI, although other studies have not confirmed this finding (43,44). Eberhardt et al. (45) demonstrated in the Bronx Longitudinal Aging Study that digoxin use in the elderly without evidence of CHF was an independent predictor of mortality. The results of the DIG study trial demonstrated that digoxin could be used in older subjects with CHF, but in lower doses than previously employed in clinical practice (46).

**Diuretics**

The Joint National Committee on Detection, Evaluation, and Treatment of High Blood Pressure recommended thiazide-like diuretics or β blockers as initial drug treatment of hypertension because these drugs had been demonstrated to reduce cardiovascular morbidity and mortality in controlled clinical trials (47). Moreover, the results of the Systolic Hypertension in the Elderly (SHEP) trial specifically showed the safety and efficacy of a diuretic and a β blocker in the treatment of isolated systolic hypertension in the elderly (48). In the elderly, a blanket recommendation for the starting medication in the treatment of hypertension is ill-advised, in part, because of the presence of comorbid conditions. For example, in older hypertensive patients with CHF and a reduced LV ejection fraction (49–53) or in those elderly patients with CHF with a normal LV ejection fraction (53–55), therapy should include a diuretic, an ACE inhibitor, and a β blocker.
Loop diuretics remain first-line drug therapy in the treatment of patients with decompensated CHF. Diuretics are multifaceted in their effect in CHF. First, they effect a reduction in plasma volume by triggering a time-dependent natriuretic response. This drop in plasma volume reduces venous return and thereby decreases ventricular filling pressures. These volume changes facilitate relief of congestive symptomatology, such as peripheral and/or pulmonary edema. Intravenous loop-diuretic therapy has also been shown to increase central venous capacitance, which may further contribute to improvement in congestive symptomatology. Both loop and thiazide-like diuretics undergo a mixed pattern of renal or hepatic elimination with the component of renal clearance being responsible for diuresis (56). Age-related decreases in renal function may reduce the efficacy of conventional doses of diuretics in elderly patients. This “renal function-related resistance” can be easily overcome, if recognized, by careful upward titration of the diuretic dose. Resistance to diuretic effect in CHF may also derive from a pattern of variable and unpredictable absorption, particularly with the loop diuretic furosemide. This issue is resolvable with the use of a predictably absorbed loop diuretic such as torsemide (57).

A thiazide-like diuretic, such as hydrochlorothiazide, may be used in the occasional older patient with mild CHF. However, thiazide-like diuretics have diminished effectiveness at conventional doses when the glomerular filtration rate falls below 30 mL/min; accordingly, older patients with moderate-to-severe CHF should be treated with a loop diuretic such as furosemide. Older patients with severe CHF or concomitant significant renal insufficiency may need combination diuretic therapy employing a loop diuretic together with the thiazide-like diuretic metolazone (56). The slowly and erratically absorbed form of metolazone (Zaroxlyn®) is the preferred form when combination therapy is being considered. Nonsteroidal anti-inflammatory drugs (NSAIDs) may decrease both the antihypertensive and natriuretic effect of loop diuretics (56). This is a particular problem when loop diuretics are employed to manage CHF-related congestive symptomatology (58). A final consideration is the sometimes insidious manner by which NSAIDs can interact with diuretics in that several commonly used NSAIDs are now available over the counter.

Serum electrolytes need to be closely monitored in older patients treated with diuretics. Hypokalemia and/or hypomagnesemia, both of which may precipitate ventricular arrhythmias and/or digitalis toxicity, can occur with diuretic therapy (59). Hyponatremia is not uncommon in the elderly treated with diuretics, particularly when thiazide-like diuretics are being employed (60). Older patients with CHF are especially sensitive to volume depletion with dehydration, hypotension, and prerenal azotemia occurring in the face of excessive diuretic effect. Older patients with CHF and normal LV ejection fraction should receive diuretics more cautiously.

**β-Adrenergic Blockers**

β Blockers are used in various cardiovascular disorders, with resultant beneficial and adverse effects (61). β Blockers are very effective antianginal agents in older, as well as younger, patients. Combined therapy with β blockers and nitrates may be more beneficial in the treatment of angina pectoris than either drug used alone (61).

Diuretics or β blockers have been recommended as initial drug therapy for hypertension in older persons because these drugs have been shown to decrease cardiovascular morbidity and mortality in controlled clinical trials (47,62). β Blockers are especially useful in the treatment of hypertension in older patients who have had a prior MI, angina pectoris, silent myocardial ischemia, complex ventricular arrhythmias, supraventricular tachyarrhythmias, or hypertrophic cardiomyopathy.
Teo et al. (63) analyzed 55 randomized controlled trials that investigated the use of β blockers in patients after MI. Mortality was significantly decreased (19%) in patients receiving β blockers, compared with control patients. In the Beta Blocker Heart Attack Trial (BHAT), propranolol significantly decreased total mortality by 34% in patients aged 60 to 69 years, and insignificantly reduced total mortality by 19% in patients aged 30 to 59 years (64). In the Norwegian Timolol Study, timolol significantly decreased total mortality by 43% in postinfarction patients aged 65 to 75 years, and significantly reduced total mortality by 34% in postinfarction patients younger than 65 years (65). Despite the utility of β blockers in post-MI patients, they are still underutilized in older patients (66–68).

β Blockers decrease complex ventricular arrhythmias including ventricular tachycardia (69–72). β Blockers also increase the ventricular fibrillation threshold in animal models and have been shown to reduce the incidence of ventricular fibrillation in patients with acute MI (73). A randomized, double-blind, placebo-controlled study of propranolol in high-risk survivors of acute MI at 12 Norwegian hospitals demonstrated that patients treated with propranolol for one year had a statistically significant 52% decrease in sudden cardiac death (70).

In addition, β blockers decrease myocardial ischemia (71,72,74), which may reduce the likelihood of ventricular fibrillation. Stone et al. (74) demonstrated by 48-hour ambulatory ECGs in 50 patients with stable angina pectoris that propranolol, not diltiazem or nifedipine, caused a significant decrease in the mean number of episodes of myocardial ischemia and in the mean duration of myocardial ischemia compared with placebo. Furthermore, β blockers reduce sympathetic tone.

Studies have demonstrated that β blockers reduce mortality in older and younger patients with complex ventricular arrhythmias and heart disease (Table 4) (64,71,72,75–77). In the BHAT of 3290 patients comparing propranolol with placebo, propranolol reduced sudden cardiac death by 28% in patients with complex ventricular arrhythmias and by 16% in patients without ventricular arrhythmias (64).

Hallstrom et al. (75) did a retrospective analysis of the effect of antiarrhythmic drug use in 941 patients resuscitated from prehospital cardiac arrest due to ventricular fibrillation between 1970 and 1985. β blockers were administered to 28% of the patients, and no antiarrhythmic drug to 39%. There was a reduced incidence of death or recurrent cardiac arrest in patients treated with β blockers versus no antiarrhythmic drug (relative risk 0.47; adjusted relative risk 0.62).

Aronow et al. (76) performed a prospective study in 245 elderly patients (mean age 81 years) with heart disease (64% with prior MI and 36% with hypertensive heart disease), complex ventricular arrhythmias diagnosed by 24-hour ambulatory ECGs, and LV ejection fraction greater than 40%. Nonsustained ventricular tachycardia occurred in 32% of patients. Myocardial ischemia occurred in 33% of patients. Mean follow-up was 30 months in patients randomized to propranolol and 28 months in patients randomized to no antiarrhythmic drug. Propranolol was discontinued because of adverse effects in 11% of patients. Follow-up 24-hour ambulatory ECGs showed that propranolol was significantly more effective than no antiarrhythmic drug in reducing ventricular tachycardia (>90%), in decreasing the average number of ventricular premature complexes per hour (>70%), and in abolishing silent ischemia.

Multivariate Cox regression analysis showed that propranolol caused a significant 47% decrease in sudden cardiac death, a significant 37% reduction in total cardiac death, and an insignificant 20% decrease in total death (71). Univariate Cox regression analysis showed that the reduction in mortality and complex ventricular arrhythmias in elderly patients with heart disease taking propranolol was due more to an anti-ischemic effect than to an antiarrhythmic effect (72). Table 4 also shows that there was a circadian
### Table 4  Effect of β Blockers on Mortality in Elderly Patients with Complex Ventricular Arrhythmias and Heart Disease

<table>
<thead>
<tr>
<th>Study</th>
<th>Age (yr)</th>
<th>Mean follow-up (mo)</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>BHAT</td>
<td>60–69 (33%)</td>
<td>25</td>
<td>Compared with placebo, propranolol reduced sudden cardiac death by 28% in patients with complex VA and 16% in patients without VA.</td>
</tr>
<tr>
<td>Hallstrom</td>
<td>62 (mean)</td>
<td>108</td>
<td>Reduced incidence of death or recurrent cardiac arrest in patients treated with β blockers vs. no antiarrhythmic drug (adjusted relative risk 0.62).</td>
</tr>
<tr>
<td>Aronow et al.</td>
<td>62–96 (mean 81)</td>
<td>29</td>
<td>Compared with no antiarrhythmic drug, propranolol caused a 47% significant decrease in sudden cardiac death, a 37% significant reduction in total cardiac death, and a 20% insignificant decrease in total death.</td>
</tr>
<tr>
<td>Aronow et al.</td>
<td>62–96 (mean 81)</td>
<td>29</td>
<td>Among patients taking propranolol, suppression of complex VA caused a 33% reduction in sudden cardiac death, a 27% decrease in total cardiac death, and a 30% reduction in total death; abolition of silent ischemia caused a 70% decrease in sudden cardiac death, a 72% reduction in total cardiac death, and a 69% decrease in total death.</td>
</tr>
<tr>
<td>Aronow et al.</td>
<td>62–96 (mean 81)</td>
<td>29</td>
<td>Incidence of sudden cardiac death or fatal myocardial infarction was significantly increased between 6 and 12 a.m., with peak hour at 8 a.m. and secondary peak at 7 p.m. in patients with no antiarrhythmic drug; propranolol abolished the circadian distribution of sudden cardiac death or fatal myocardial infarction.</td>
</tr>
<tr>
<td>CAST</td>
<td>66–79 (40%)</td>
<td>12</td>
<td>Patients on β blockers (30% of study group) had a significant reduction in all-cause mortality of 43% at 30 days, 46% at 1 year, and 33% at 2 years: in patients on β blockers, arrhythmic death or cardiac arrest was significantly reduced by 66% at 30 days, 53% at 1 year, and 36% at 2 years; multivariate analysis showed β blockers to be an independent factor for reduced arrhythmic death or cardiac arrest by 40% and for all-cause mortality by 33%.</td>
</tr>
</tbody>
</table>

**Abbreviations:** BHAT, Beta Blocker Heart Attack Trial; VA, ventricular arrhythmias; CAST, Cardiac Arrhythmia Suppression Trial.

**Source:** From Refs. 64, 71, 72, 75–77, and 183.
distribution of sudden cardiac death or fatal MI, with the peak incidence occurring from 6 a.m. to 12 a.m. (peak hour 8 a.m. and secondary peak around 7 p.m.) in patients treated with no antiarrhythmic drug (76). Propranolol abolished this circadian distribution of sudden cardiac death or fatal MI (76).

In a retrospective analysis of data from the Cardiac Arrhythmia Suppression Trial (CAST), Kennedy et al. (77) found that 30% of patients with an LV ejection fraction less than 40% were receiving β blockers. Forty percent of these 1735 patients were between 66 and 79 years old. Patients on β blockers had a significant reduction in all-cause mortality of 43% within 30 days, 46% at one year, and 33% at two years. Patients receiving β blockers also had a significant decrease in arrhythmic death or cardiac arrest of 66% at 30 days, 53% at one year, and 36% at two years. Multivariate analysis showed that β blockers were an independent factor for reducing arrhythmic death or cardiac arrest by 40%, for decreasing all-cause mortality by 33%, and for reducing the occurrence of new or worsening CHF by 32%. On the basis of these data (64,71,72,75–77), β blockers can be utilized in the treatment of older and younger patients with ventricular tachycardia or complex ventricular arrhythmias associated with ischemic or nonischemic heart disease, and with normal or abnormal LV ejection fraction, if there are no absolute contraindications to the drugs.

β Blockers are also useful in the treatment of supraventricular tachyarrhythmias in older and younger patients (78,79). If a rapid ventricular rate associated with atrial fibrillation persists at rest or during exercise despite digoxin therapy, then verapamil (80) diltiazem (81) or a β blocker (82) should be added to the therapeutic regimen. These drugs act synergistically with digoxin to depress conduction through the atrioventricular junction. The initial oral dose of propranolol is 10 mg q6h, which can be increased to a maximum of 80 mg q6h, if necessary.

β Blockers have been demonstrated to reduce mortality in older persons with New York Heart Association (NYHA) class II-IV CHF and abnormal LV ejection fraction treated with diuretics and ACE inhibitors with or without digoxin (52,53,83–87). β Blockers have also been shown to reduce mortality in older persons with NYHA class II-III CHF and normal LV ejection fraction treated with diuretics plus ACE inhibitors (53,55,86,87). Numerous drug interactions have been reported with β blockers in the elderly (61). Recently, quinidine, a known inhibitor of CYP2D6, was shown to decrease the hepatic metabolism of topically applied ophthalmic timolol, with resultant exaggeration of the β-blocking effect of timolol (88).

ACE Inhibitors

ACE inhibitors are effective antihypertensive agents. A meta-analysis of 109 treatment studies showed that ACE inhibitors are more effective than other antihypertensive drugs in decreasing LV mass (89). Older hypertensive patients with CHF associated with abnormal (49–51) or normal (54) LV ejection fraction, LV hypertrophy, or diabetes mellitus, should initially be treated with an ACE inhibitor. ACE inhibitors reduce mortality in patients with CHF associated with abnormal LV ejection fraction (49–51). The Survival and Ventricular Enlargement (SAVE) trial (90) and the combined Studies of Left Ventricular Dysfunction (SOLVD) treatment and prevention trials (91) also demonstrated that ACE inhibitors such as captopril or enalapril should be standard therapy for most patients with significant LV systolic dysfunction with or without CHF. In addition, ACE inhibitor therapy has been shown to be beneficial in the treatment of elderly patients (mean age 80 years) with CHF caused by prior MI associated with normal LV ejection fraction (54). High-dose ACE inhibitor therapy remains the standard of care.
in the management of CHF. Low-dose ACE inhibitor therapy has been studied in CHF, but with less favorable results. For example, a recent trial compared low (2.5–5.0 mg/day) with high-dose lisinopril (32.5–35.0 mg/day), with the latter being associated with a more significant reduction in mortality and all-cause hospitalization rate (92).

An observational prospective study was performed in 477 patients (mean age 79 years) with prior MI and an asymptomatic LV ejection fraction of less than 40% (mean LV ejection fraction 31%) (93). At 34-month follow-up, patients treated with ACE inhibitors without β blockers had a 17% significant reduction in new coronary events and a 32% significant reduction in CHF (93). At 34-month follow-up, patients treated with β blockers without ACE inhibitors had a 25% significant reduction in new coronary events and a 41% significant reduction in CHF (93). At 41-month follow-up, patients treated with both β blockers and ACE inhibitors had a significant 37% reduction in new coronary events and a significant 60% reduction in CHF (93).

Treatment with ACE inhibitors should be initiated in elderly patients in low doses after correction of hyponatremia or volume depletion. It is important to avoid overdiuresis before beginning therapy with ACE inhibitors since volume depletion may cause hypotension or renal insufficiency when ACE inhibitors are begun or when the dose of these drugs is increased to full therapeutic levels. After the maintenance dose of ACE inhibitor is reached, it may be necessary to increase the dose of diuretics. The initial dose of enalapril is 2.5 mg daily and of captopril is 6.25 mg TID. The maintenance doses are 5 to 20 mg daily and 25 to 50 mg TID, and the maximum doses are 20 mg BID and 150 mg TID, respectively.

Older patients at risk for excessive hypotension should have their blood pressure monitored closely for the first two weeks of ACE inhibitor or angiotensin II receptor blocking therapy, and, thereafter, whenever the dose of ACE inhibitor or diuretic is increased. Renal function should be monitored in patients on ACE inhibitors to detect increases in blood urea nitrogen and serum creatinine, especially in older patients with renal artery stenosis. A rise in serum creatinine in an ACE inhibitor treated CHF patient is not uncommonly the result of ACE inhibitor-induced alterations in renal hemodynamics. There is no specific rise in serum creatinine where corrective actions need be taken although logic would suggest that the greater the increment in serum creatinine the more important the intervention. Typically, reducing or temporarily discontinuing diuretics and/or liberalizing sodium intake are sufficient measures to return renal function to baseline. Not uncommonly though, the administered ACE inhibitor is either stopped or the dose reduced. In most instances, ACE inhibitor therapy can be safely resumed as long as careful attention is paid to patient volume status (94). Potassium-sparing diuretics or potassium supplements should be carefully administered to patients receiving ACE inhibitor therapy because of the attendant risk of hyperkalemia. In this regard, the Randomized Aldactone Evaluation Study (RALES) showed in persons with severe CHF treated with diuretics, ACE inhibitors, and digoxin that compared with placebo, spironolactone 25 mg/day did not carry an excessive risk of hyperkalemia while resulting in a significant reduction in mortality and hospitalization for CHF (95).

Angiotensin-II Receptor Blockers

Angiotensin-II receptor blockers (ARBs) have been studied fairly extensively in hypertension (96–98), diabetic nephropathy (99), and CHF (100), with results comparable to those seen when these disease states are treated with ACE inhibitors. Although the published experience with these drugs in the elderly is limited, the drugs appear to be safe if used with similar precautions as those recommended for ACE inhibitors, as described above (96,98). These drugs are noteworthy in that they have a more favorable side-effect profile
and, in particular, are not associated with cough, a fairly common side effect with ACE inhibitor therapy (97). Likewise, in the Losartan Heart Failure Survival Study (ELITE II), losartan was associated with fewer adverse effects than was captopril (101). Outcomes of studies are supportive of ARBs, such as losartan and irbesartan, being superior to conventional non-ACE-inhibitor-based therapy in decreasing end-stage renal failure event rates in patients with type II diabetic nephropathy (102,103). In CHF the hope that ARBs are more effective therapy than ACE inhibitors has not been realized, as of yet, though additional studies are underway to establish the positioning of ARBs in current HF regimens.

Direct Renin Inhibitors

Aliskiren is a nonpeptide direct renin inhibitor and is the first drug of this class to be approved for clinical use in systemic hypertension (see chapter 5, “Systemic Hypertension in the Elderly”) (104). The drug is approved for once-daily use as a monotherapy and for combination use with other antihypertensive drugs.

There is no dose adjustment necessary in elderly patients or in patients with hepatic or renal insufficiency (105). The most common side effects of aliskiren are a lower incidence of headache, nasopharyngitis, dizziness, and diarrhea. The drug is not associated with an increased incidence of cough (106). Angioedema is a rare complication of therapy and appears to occur at a lower frequency than with ACE inhibitors (106).

Pharmacokinetic studies with aliskiren have shown no relevant drug-drug interactions with warfarin, digoxin, amlodipine, valsartan, and ramipril (107,108). With the combination of aliskiren and furosemide, there are decreased levels of the diuretic (105).

Nitrates

Nitrates are effective therapies for older individuals; however, caution should always be used because of the associated dangers of orthostatic hypotension, syncope, and falls, especially if the treatment is combined with diuretics and other vasodilators. Recently, it was shown that nitrate headaches are less frequent in older patients and in individuals with renal dysfunction (109). It has also been shown that the use of the thiazolidinedione rosiglitazone may increase the risk of myocardial ischemia in patients taking concomitant nitrate therapy.

Calcium Channel Blockers

Calcium channel blockers are effective antihypertensive and antianginal drugs in older patients. Verapamil (80) and diltiazem (81) are especially valuable in treating hypertensive patients who also have supraventricular tachyarrhythmias. However, recent reports have suggested an increased mortality risk with calcium channel blockers, especially with the use of short-acting dihydropyridines in older subjects (110–112). With the use of longer-acting calcium blockers, such as the dihydropyridine nitrendipine, a strong mortality benefit was seen in patients with isolated systolic hypertension (113), although many were receiving concurrent β-blocker therapy. In contrast, nisoldipine was shown to be less effective in protecting against cardiovascular mortality in diabetic patients with hypertension when compared with an enalapril-treated group (114).

Verapamil improved exercise capacity, peak LV filling rate, and a clinicoradiographic HF score in patients with CHF, normal LV ejection fraction, and impaired LV diastolic filling (115). However, calcium channel blockers, such as verapamil, diltiazem, and nifedipine, may exacerbate CHF in patients with associated abnormal LV ejection fraction (116). In addition, some calcium channel blockers have been shown to increase mortality in
patients with CHF and abnormal LV ejection fraction after MI (117). Therefore, calcium channel blockers such as verapamil, diltiazem, and nifedipine may be used to treat older patients with CHF associated with normal LV ejection fraction, but are contraindicated in treating older patients with CHF associated with abnormal LV ejection fraction.

Amlodipine and felodipine are two vasculospecific dihydropyridine agents that appear to be safer in patients having CHF, although neither of these drugs should be used to treat CHF(28).

The age-associated decrease in hepatic blood flow and hepatic metabolic capacity may result in higher serum concentrations of verapamil, diltiazem, and nifedipine (118). Therefore, these drugs should be given to older persons in lower starting doses and titrated carefully.

**α-Adrenergic Blockers**

α-Adrenergic blockers are effective treatments for patients with hypertension and have become first-line treatments for males with symptomatic prostatism. Caution should be exercised when using these agents because of a significant incidence of postural hypotension, especially in patients receiving diuretics or other vasodilator drugs (119,120). A more selective α1 blocker, tamsulosin, is now available, which improves prostatism symptoms without having vasodilator effects (121). However, the National Heart, Lung, and Blood Institute withdrew doxazosin from the Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack (ALLHAT) trial after an interim analysis showed a 25% greater rate of a secondary endpoint, combined cardiovascular disease in patients on doxazosin than in those on chlorthalidone, largely driven by the increased risk of CHF (122). These findings have cast a shroud over the use of doxazosin in the elderly, particularly if it is being contemplated as monotherapy in a hypertensive elderly patient.

**Lidocaine**

Intravenous lidocaine may be used to treat complex ventricular arrhythmias during acute MI (78). Lidocaine toxicity is more common in the elderly and older patients should be monitored for dose-related confusion, tinnitus, paresthesias, slurred speech, tremors, seizures, delirium, respiratory depression, and hypotension. Older patients with CHF or impaired liver function are at increased risk for developing central nervous system adverse effects from lidocaine (123). In these patients, the loading dose should be decreased by 25–50%, and any maintenance infusion should be initiated at a rate of 0.5 to 2.5 mg/min, with the patient monitored closely for adverse effects. The dose of lidocaine should also be reduced if the patient is receiving β blockers (124) or cimetidine, since these drugs reduce the metabolism of lidocaine.

**Other Antiarrhythmic Drugs**

The use of antiarrhythmic drugs in the elderly is extensively discussed elsewhere (79,125). In the CAST I trial, encainide and flecainide significantly increased mortality in survivors of MI with asymptomatic or mildly symptomatic ventricular arrhythmias, when compared with placebo (126). In the CAST II, moricizine insignificantly increased mortality when compared with placebo (127). Akiyama et al. (128) found that older age increased the likelihood of adverse events, including death, in patients treated with encainide, flecainide, or moricizine in these two studies.

In a retrospective analysis of the effect of empirical antiarrhythmic treatment in 209 cardiac arrest patients who were resuscitated out of hospital, Moosvi et al. (129)
found that the two-year mortality was significantly lower for patients treated with no antiarrhythmic drug than for patients treated with quinidine or procainamide. Hallstrom et al. (75) showed an increased incidence of death or recurrent cardiac arrest in patients treated with quinidine or procainamide versus no antiarrhythmic drug.

In a prospective study of 406 elderly subjects (mean age 82 years) with heart disease (58% with prior MI) and asymptomatic complex ventricular arrhythmias, the incidence of sudden cardiac death, total cardiac death, and total mortality were not significantly different in patients treated with quinidine or procainamide or with no antiarrhythmic drug (130). In this study, quinidine or procainamide did not reduce mortality in comparison with no antiarrhythmic drug in elderly patients with presence versus absence of ventricular tachycardia, ischemic or nonischemic heart disease, and abnormal or normal LV ejection fraction. The incidence of adverse events causing drug cessation in elderly patients in this study was 48% for quinidine and 55% for procainamide.

A meta-analysis of six double-blind studies of 808 patients with chronic atrial fibrillation who underwent direct current cardioversion to sinus rhythm demonstrated that the one-year mortality was significantly higher in patients treated with quinidine than in patients treated with no antiarrhythmic drug (131). In the Stroke Prevention in Atrial Fibrillation Study, arrhythmic death and cardiac mortality were also significantly increased in patients receiving antiarrhythmic drugs compared with patients not receiving antiarrhythmic drugs, especially in patients with a history of CHF (132).

Teo et al. (63) analyzed 59 randomized controlled trials comprising 23,229 patients that investigated the use of class I antiarrhythmic drugs after MI. Patients receiving class I antiarrhythmic drugs had a significantly higher mortality than patients receiving no antiarrhythmic drugs. None of the 59 trials demonstrated that a class I antiarrhythmic drug decreased mortality in postinfarction patients. Therefore, it is currently not recommended that class I antiarrhythmic drugs be used for the treatment of ventricular tachycardia or complex ventricular arrhythmias associated with heart disease.

Amiodarone is very effective in suppressing ventricular tachycardia and complex ventricular arrhythmias. However, there are conflicting data about the effect of amiodarone on mortality (133–140). The Veterans Administration Cooperative Study comparing amiodarone versus placebo in HF patients with malignant ventricular arrhythmias recently showed that amiodarone was very effective in decreasing ventricular tachycardia and complex ventricular arrhythmias, but it did not affect mortality (139).

In the Sudden Cardiac Death in Heart Failure Trial, 2521 patients, mean age 60 years, with NYHA class II or III HF, a LV ejection fraction of 35% or less and a mean QRS duration on the resting ECG of 120 milliseconds, were randomized to placebo, amiodarone, or an implantable cardioverter-defibrillator (ICD) (140). At 46-month median follow-up, compared with placebo, amiodarone insignificantly increased mortality by 6% but ICD therapy significantly reduced all-cause mortality by 23% (140).

The incidence of adverse effects from amiodarone has been reported to approach 90% after five years of treatment (141). In the Cardiac Arrest in Seattle: Conventional Versus Amiodarone Drug Evaluation Study, the incidence of pulmonary toxicity was 10% at two years in patients receiving an amiodarone dose of 158 mg daily (142). On the basis of these data, one should reserve the use of amiodarone for the treatment of life-threatening ventricular tachyarrhythmias or in patients who cannot tolerate or who do not respond to β-blocker therapy.

Amiodarone is also the most effective drug for treating refractory atrial fibrillation in terms of converting atrial fibrillation to sinus rhythm and slowing a rapid ventricular rate. However, because of the high incidence of adverse effects caused by amiodarone, it
should be used in low doses in patients with atrial fibrillation when life-threatening atrial fibrillation is refractory to other therapy (143).

**Lipid-Lowering Drugs**

The safety of lipid-lowering drugs, specifically 3-hydroxy-3-methylglutaryl-coenzyme A (HMG CoA) reductase inhibitors (statins), was demonstrated in the Cholesterol Reduction in Seniors Program (CRISP) (144). Furthermore, a meta-analysis of 14 randomized trials of statins from 90,056 participants confirmed the safety and efficacy of statins (145).

In the Scandinavian Simvastatin Survival Study, 1,464,444 men and women with coronary artery disease were treated with double-blind simvastatin or placebo. At 5.4-years follow-up, patients treated with simvastatin had a 35% decrease in serum low-density lipoprotein (LDL) cholesterol, a 25% reduction in serum total cholesterol, an 8% increase in serum high-density lipoprotein (HDL) cholesterol, a 34% decrease in major coronary events, a 42% reduction in coronary deaths, and a 30% decrease in total mortality. In patients aged 65 to 70 years, simvastatin reduced all-cause mortality by 35%, coronary artery disease mortality by 43%, major coronary events by 34%, nonfatal MI by 33%, any atherosclerosis-related endpoint by 34%, and coronary revascularization by 41% (147). The absolute risk reduction for both all-cause mortality and coronary artery disease mortality was approximately twice as great in persons aged 65 to 70 years compared with persons younger than 65 years (147).

In the Cholesterol and Recurrent Events Trial (148), 4159 men and women aged 21 to 75 years (1283 aged 65–75 years) with MI, serum total cholesterol levels less than 250 mg/dL, and serum LDL cholesterol levels greater than or equal to 115 mg/dL were treated with double-blind pravastatin and placebo. At five-year follow-up, patients treated with pravastatin had a 32% reduction in serum LDL cholesterol, a 20% decrease in serum total cholesterol and a 5% increase in serum HDL cholesterol. Pravastatin reduced coronary artery disease death or nonfatal MI significantly by 39% in persons aged 65 to 75 years, and insignificantly by 13% in persons younger than 65 years (148). Pravastatin decreased major coronary events significantly by 32% in persons aged 65 to 75 years and significantly by 19% in persons younger than 65 years. It also reduced stroke significantly by 40% in persons aged 65 to 75 years and insignificantly by 20% in persons younger than 65 years. Pravastatin decreased coronary revascularization significantly by 32% in persons aged 65 to 75 years, and significantly by 25% in persons younger than 65 years. For every 1000 persons treated with pravastatin for five years, 225 cardiovascular events would be prevented in persons aged 65 to 75 years and 121 cardiovascular events would be prevented in persons younger than 65 years (148).

In the Prospective Study of Pravastatin in the Elderly at Risk (PROSPER) trial, a randomized, placebo-controlled study of 5804 men and 3000 women, pravastatin 40 mg/day was shown to lower LDL concentrations by 34% in subjects 70 to 82 years of age. In this study, drug treatment reduced coronary heart disease death (CHD) and nonfatal MI. No benefit on stroke prevention was seen, and there were more cancer diagnoses with pravastatin. However, incorporation of this latter finding in a meta-analysis showed no overall increase in cancer risk (149).

The Long-Term Intervention with Pravastatin in Ischaemic Disease study randomized 9014 persons with a history of MI or unstable angina who had initial serum total cholesterol levels of 155 to 271 mg/dL to pravastatin 40 mg daily or placebo (150). At eight-year follow-up of 3514 persons aged 65 to 75 years at study entry, compared with placebo, pravastatin significantly reduced all-cause mortality by 21%, death from CHD by 24%, fatal
and nonfatal MI by 26%, death from cardiovascular disease by 26%, need for coronary artery bypass graft surgery by 26%, and need for coronary angioplasty by 34% (150).

The Heart Protection Study randomized 20,536 men and women (5806 of whom were aged 70–80 years) with prior MI (8510 persons), other CHD (4876 persons), and no CHD (7150 persons) and a serum total cholesterol level of 135 mg/dL or higher to simvastatin 40 mg daily or to placebo (151). Of the 7150 persons without CHD, 25% had cerebrovascular disease, 38% had peripheral arterial disease (PAD), 56% had diabetes mellitus, and 3% had only treated hypertension without atherosclerotic vascular disease or diabetes mellitus. At five-year follow-up, compared with placebo, simvastatin significantly reduced all-cause mortality by 13%, any cardiovascular death by 17%, major coronary events by 27%, any stroke by 25%, coronary or noncoronary revascularization by 24%, and any major cardiovascular event by 24% (151). These significant reductions in mortality and in cardiovascular events occurred regardless of initial levels of serum lipids, age, or gender. First major cardiovascular event was significantly reduced by simvastatin by 24% in persons younger than 65 years, by 23% in persons aged 65 to 69 years, and by 18% in persons aged 70 to 80 years at study entry (151). Five years of simvastatin treatment prevented MI, stroke, and revascularization in 70 to 100 persons per 1000 treated persons (151).

Sixty-nine elderly patients, mean age 75 years, with intermittent claudication due to PAD were randomized to simvastatin 40 mg daily or placebo (152). Compared with placebo, simvastatin significantly increased treadmill exercise time until the onset of intermittent claudication by 24% at six months after treatment and by 42% at one year after treatment.

Observational data have also demonstrated in 1410 men and women, mean age 81 years, with CHD and hypercholesterolemia that at three-year follow-up, use of statins significantly reduced CHD death or nonfatal MI by 50% (153), stroke by 60% (154), and CHF by 48% (155). The lower the reduction in serum LDL cholesterol, the greater the reduction in coronary events (153) and in stroke (154). Statins also significantly reduced new coronary events by 37% and new stroke by 47% in 529 men and women, mean age 79 years, with diabetes mellitus, prior MI, and hypercholesterolemia at 29-month follow-up (156). In addition, statins significantly reduced new coronary events by 52% in persons with prior MI and by 59% in persons with no prior MI in 660 men and women with PAD and hypercholesterolemia at 39-month follow-up (157).

On the basis of the available data showing increased risk of cardiovascular disease from abnormal lipoprotein patterns (158), dietary therapy for older patients with dyslipidemia, regardless of age, in the absence of other serious life-limiting illnesses, such as cancer, dementia, or malnutrition, is recommended (159). If hyperlipidemia persists after three months of dietary therapy, hypolipidemic drugs should be considered, depending on serum lipid levels, presence or absence of coronary artery disease, presence or absence of other coronary risk factors, and the patient’s overall clinical status. This approach is consistent with the recent National Cholesterol Education Program Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults recommendations in males aged 65 years and older and females aged 75 years and older. (160). In older men and women, the HMG-CoA reductase inhibitors would be the drugs of choice for treating a high-serum LDL cholesterol level.

Recent data have demonstrated that the serum LDL cholesterol should be reduced to less than 70 mg/dL in high-risk persons regardless of age or gender (161–163). The updated National Cholesterol Education Program (NCEP) III guidelines state that in very high-risk patients, a serum LDL cholesterol level of less than 70 mg/dL is a reasonable clinical strategy (164). When a high-risk person has hypertriglyceridemia or low serum HDL cholesterol, consideration can be given to combining a fibrate or nicotinic acid with an LDL cholesterol–lowering drug (164). For moderately high-risk persons (two or more
risk factors and a 10-year risk for CHD of 10% to 20%), the serum LDL cholesterol should be reduced to less than 100 mg/dL (164). When LDL cholesterol–lowering drug therapy is used to treat high-risk persons or moderately high-risk persons, the serum LDL cholesterol should be reduced by at least 30–40% (164).

**Anticoagulants**

Anticoagulant therapy in the elderly is discussed extensively elsewhere (79,165). Anticoagulants are effective in the prevention and treatment of many thromboembolic disorders including venous thromboembolism and pulmonary embolism, acute MI and embolism associated with prosthetic heart valves or atrial fibrillation. These conditions, necessitating the use of anticoagulants, are more common in elderly than in younger patients. In the report from the Sixty Plus Reinfarction Group who evaluated the effects of oral anticoagulant therapy on total mortality after MI in patients older than 60 years, it was shown that active therapy lowered both mortality and reinfarction compared with placebo (166). However, the treatment group also had more major bleeding complications.

The anticoagulant response to warfarin is increased with age (167). Chronic diseases, which increase the risk for bleeding during anticoagulant therapy, are also more common in elderly patients than in younger patients. In addition, elderly patients are at higher risk for bleeding during anticoagulant therapy because of increased vascular or endothelial fragility (168). Furthermore, older patients may be at increased risk for bleeding due to anticoagulant therapy because they may be taking other drugs that potentiate the anticoagulant effect. Drugs such as aspirin, cephalosporins, and penicillins increase the risk of bleeding in patients treated with heparin. Drugs such as allopurinol, amiodarone, aspirin, cimetidine, ciprofloxacin, clofibrate, cotrimoxazole, dextropropoxyphene, disulfiram, erythromycin, fluconazole, isoniazid, ketoconazole, meclofenamic acid, metronidazole, miconazole, norfloxacin, phenylbutazone, phenytoin, quinidine, sulfipyrazone, sulindac, thyroxine, and trimethoprim-sulfamethoxazole potentiate the effect of warfarin, causing an increased prothrombin time and risk of bleeding.

**ADVERSE EFFECTS OF DRUGS IN THE ELDERLY**

Cardiovascular drugs are often associated with adverse effects that simulate common disorders in the elderly (Table 5). In addition, there are important drug-disease interactions (Table 6), drug-drug interactions (Table 7), and drug-alcohol interactions (169) (Table 8) that occur in older patients.

<table>
<thead>
<tr>
<th><strong>Table 5</strong> Cardiovascular Drugs Regularly Detected as the Culprit in Some Common Disorders of the Elderly</th>
</tr>
</thead>
<tbody>
<tr>
<td>Disorder &lt;br&gt;Confusion states &lt;br&gt;Tinnitus, vertigo &lt;br&gt;Depression &lt;br&gt;Falls &lt;br&gt;Postural hypotension &lt;br&gt;Constipation &lt;br&gt;Urinary retention &lt;br&gt;Urinary incontinence</td>
</tr>
</tbody>
</table>

*Source: From Ref. 181.*
### Table 7  Selected Clinically Significant Drug-Drug Interactions in Geriatric Patients

<table>
<thead>
<tr>
<th>Primary drugs</th>
<th>Interacting drugs</th>
<th>Mechanism of interaction</th>
<th>Possible effects</th>
</tr>
</thead>
<tbody>
<tr>
<td>Augmented drug effects</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Antidiabetic sulfonlureas</td>
<td>Chloramphenicol, Warfarin, Phenylbutazone</td>
<td>IM</td>
<td>Hypoglycemia</td>
</tr>
<tr>
<td>(tolbutamide, chlorpropamide)</td>
<td>Allopurinol</td>
<td>IM</td>
<td>Bone marrow suppression</td>
</tr>
<tr>
<td></td>
<td>Diltiazem, verapamil</td>
<td>IM</td>
<td>Increase serum carbamazepine concentration and risk of toxicity (e.g., nausea, ataxia, nystagmus)</td>
</tr>
<tr>
<td>Cyclosporine</td>
<td>Diltiazem, verapamil</td>
<td>IM</td>
<td>Increase serum cyclosporine concentration and risk of toxicity (e.g., hepato- and nephrotoxicity)</td>
</tr>
<tr>
<td>Digoxin</td>
<td>Amiodarone, diuretics, quinidine, verapamil</td>
<td>OM</td>
<td>Increase serum digoxin concentration and risk of toxicity (e.g., nausea, confusion, cardiotoxicity)</td>
</tr>
<tr>
<td>Disopyramide</td>
<td>Diltiazem, verapamil</td>
<td>OM</td>
<td>Bradycardia</td>
</tr>
<tr>
<td>Lidocaine</td>
<td>β blockers, cimetidine</td>
<td>HBF</td>
<td>Increase serum lidocaine concentration and risk of toxicity (e.g., sedation, seizures, cardiotoxicity)</td>
</tr>
</tbody>
</table>

**Abbreviations:** NSAID, nonsteroidal anti-inflammatory drug; GI, gastrointestinal.

**Source:** From Ref. 184.
### Table 7  Selected Clinically Significant Drug-Drug Interactions in Geriatric Patients (Continued)

<table>
<thead>
<tr>
<th>Primary drugs</th>
<th>Interacting drugs</th>
<th>Mechanism of interaction</th>
<th>Possible effects</th>
</tr>
</thead>
<tbody>
<tr>
<td>Methotrexate</td>
<td>Aspirin, indomethacin, phenylbutazone, probenecid, sulfinpyrazone</td>
<td>DP, IE</td>
<td>Bone marrow suppression</td>
</tr>
<tr>
<td></td>
<td>Probencid</td>
<td>IE</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Sulfinpyrazone</td>
<td>DP</td>
<td></td>
</tr>
<tr>
<td>Procaainamide</td>
<td>Diltiazem, verapamil</td>
<td>OM</td>
<td>Bradycardia</td>
</tr>
<tr>
<td>Propranolol</td>
<td>Cimetidine</td>
<td>HBF</td>
<td>Bradycardia</td>
</tr>
<tr>
<td>Phenytin</td>
<td>Amiodarone, chloramphenicol, cimetidine, fluniconazole, isoniazid, phenylbutazone</td>
<td>IM</td>
<td>Increase serum phenytin concentration and risk of toxicity (e.g., nystagmus, sedation)</td>
</tr>
<tr>
<td></td>
<td>Valproic acid, warfarin</td>
<td>DP, IM</td>
<td>Increase serum phenytin concentration and risk of toxicity (e.g., nausea, cinchonism, arrhythmias)</td>
</tr>
<tr>
<td>Quinidine</td>
<td>Diltiazem, Verapamil</td>
<td>IM</td>
<td></td>
</tr>
<tr>
<td>Warfarin</td>
<td>Aspirin, indomethacin, phenylbutazone, cimetidine, metronidazole</td>
<td>DP, IM</td>
<td>Hemorrhage</td>
</tr>
<tr>
<td></td>
<td>Phenylbutazone, sulfinpyrazone</td>
<td>DP, IM</td>
<td></td>
</tr>
<tr>
<td>Decreased drug effects</td>
<td>All medications</td>
<td>Cholestyramine</td>
<td>IA</td>
</tr>
<tr>
<td></td>
<td>Antidiabetic sulfonylureas (tolbutamide, chlorpropamide)</td>
<td></td>
<td>Decrease hypoglycemic effects</td>
</tr>
<tr>
<td></td>
<td>β Blockers (nonselective)</td>
<td>IIS, MCM, IIR, OM</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Corticosteroids, thiazide diuretics</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Digoxin</td>
<td>Sucralfate</td>
<td>IA</td>
<td>Reduce absorption of digoxin. Administer sucralfate at least 2 hrs apart from digoxin.</td>
</tr>
<tr>
<td>Lincomycin</td>
<td>Kaolin-pectin</td>
<td>IA</td>
<td>Decrease drug bioavailability</td>
</tr>
<tr>
<td>Phenytin</td>
<td>Calcium, Sucralfate</td>
<td>IA</td>
<td>Decrease serum phenytin concentration and anticonvulsant effect</td>
</tr>
<tr>
<td>Prednisone</td>
<td>Rifampin</td>
<td>SM</td>
<td>Decreased steroid effects</td>
</tr>
<tr>
<td>Quinidine</td>
<td>Barbiturates</td>
<td>SM</td>
<td>Decrease antiarrhythmic effect</td>
</tr>
<tr>
<td>Tetracycline</td>
<td>Antacids-Iron</td>
<td>IA</td>
<td>Decrease drug bioavailability</td>
</tr>
<tr>
<td>Warfarin</td>
<td>Barbiturates, carbamazepine, glutethimide, rifampin, vitamin K</td>
<td>SM</td>
<td>Loss of anticoagulant control</td>
</tr>
</tbody>
</table>

(Continued)
MEDICATIONS BEST TO AVOID IN THE ELDERLY

Careful selection of drugs and dosages of drugs in the elderly can minimize adverse outcomes while maximizing clinical improvement. In their first attempt to identify medications and doses of medication that may be best to avoid in the elderly, Beers and colleagues developed a set of explicit criteria after an extensive review of the literature and assistance from 13 well-recognized experts in geriatric medicine and pharmacology (170). These criteria included 30 statements that described medications that should...
generally be avoided in nursing home residents, as well as statements that described
doses, frequencies, and duration of medications that should generally not be exceeded.
Since the publication of the explicit criteria, several research studies have utilized these
criteria to evaluate the appropriateness of medication prescribing in the elderly (171–174).
The most striking study of this type was performed by Willcox and colleagues (174), who
reported a potentially inappropriate medication prescription in 23.5% of elderly in the
community. They were criticized, however, for applying criteria that were designed for
frail elderly patients in nursing homes to healthier elderly residents in the community,
along with criteria that need to be updated (175).

Acknowledging the limitation of this first set of criteria, Beers updated and
expanded it to encompass elderly patients who are in the ambulatory setting, as well as
medications that should be avoided in elderly known to have certain conditions (176).
With the assistance of six nationally recognized experts in geriatric medicine and
pharmacology, a set of 63 criteria was developed using the first set of criteria and a more
recent literature review. Of the 63 criteria, 28 described medications or categories of
medication that were considered to be potentially inappropriate when used by all older
patients and 35 described medications or categories of medications that were considered
to be potentially inappropriate when used by elderly patients with any of 15 known
medical conditions such as heart failure, diabetes, hypertension, asthma, and arrhythmias.
These criteria were further rated by the six panelists regarding their importance. The
panelists considered a criterion to be severe when an adverse outcome was both likely to
occur and, if it did occur, would likely lead to a clinically significant event (176). Table 9
lists the cardiac medications that were recognized by the expert panel as having the
highest severity of potential problems occurring from their use and the reasons for their
avoidance. Table 10 lists medications that were identified by the expert panel as having
the highest severity of potential problems and the reasons for their avoidance in the
elderly when certain cardiac-related conditions exist.

Although these criteria serve as useful tools for assessing the quality of prescribing
to the elderly, they do not identify all cases of potentially inappropriate prescribing. In
fact, these criteria may identify appropriate prescribing as inappropriate at times. The
latter case may particularly be likely when physicians and pharmacists carefully adjust
medication regimens for specific needs of individual patients (176).

Table 9 Medications to Avoid in Older Patients

<table>
<thead>
<tr>
<th>Medications</th>
<th>Prescribing concerns</th>
</tr>
</thead>
<tbody>
<tr>
<td>Disopyramide</td>
<td>Of all antiarrhythmics, disopyramide is the most potent negative inotrope and therefore may induce heart failure in the elderly. It is also strongly anticholinergic. When appropriate, other antiarrhythmic drugs should be used.</td>
</tr>
<tr>
<td>Digoxin&lt;sup&gt;a&lt;/sup&gt;</td>
<td>Because of decreased renal clearance of digoxin, doses in the elderly should rarely exceed 0.125 mg daily, except when treating atrial arrhythmias.</td>
</tr>
<tr>
<td>Methyldopa &amp; methyldopa/HCTZ&lt;sup&gt;a&lt;/sup&gt;</td>
<td>Methyldopa may cause bradycardia and exacerbate depression in the elderly. Alternate treatments for hypertension are generally preferred.</td>
</tr>
<tr>
<td>Ticlopidine</td>
<td>Ticlopidine has been shown to be no better than aspirin in preventing clotting and is considerably more toxic. Avoid in the elderly.</td>
</tr>
</tbody>
</table>

<sup>a</sup>Panelists believed that the severity of adverse reaction would be substantially greater when these drugs were recently started. In general, the greatest risk would be within about a one-month period.

Abbreviation: HCTZ, hydrochlorothiazide.

Source: From Ref. 187.
Although the elderly make up only 14% of our population, they receive more than 30% of all prescribed medication (177). The increased exposure of medications in the elderly may lead to higher incidence of adverse drug reactions and drug-drug interactions in this population (178).

Physiologic changes with aging may also alter the elimination of drugs that can contribute to adverse outcomes with medication usage. With these concerns in mind, several authors have suggested some steps that clinicians may employ to ensure safe prescribing (177,179,180). These suggestions include the following.

- Acquire a full history of the patient’s habits and medication use.
- Evaluate the need for drug therapy. Consider alternative non–drug approaches when appropriate.
- Know the pharmacology of the drugs prescribed.
- Start with low dose of medication and titrate up slowly.
- Titrate medication dosage according to the patient’s response.
- Minimize the number of medications used.
- Educate patients regarding proper usage of medications.
- Be aware of medication cost, which may have an impact on compliance.
- Provide patient with a portable prescription record.
- Review the treatment plan regularly and discontinue medications no longer needed.

With proper monitoring and adequate understanding of the effects of medications in the elderly, the use of medication can be a positive experience for both the elderly patient and the clinician.

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5
Systemic Hypertension in the Elderly

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INTRODUCTION

There is strong evidence from large, well-controlled clinical trials which indicates that elderly patients with either combined systolic and diastolic hypertension or isolated systolic hypertension (ISH) benefit greatly from pharmacological blood pressure reduction (1). These studies demonstrate that treatment can reduce the risk of both cardiovascular and cerebrovascular morbidity. This chapter first reviews the pathophysiology of hypertension in the elderly and the rationale for both nonpharmacological and pharmacological treatments.

HYPERTENSION IN THE ELDERLY

Elderly hypertensive patients differ from young hypertensive patients in several respects. It is important to be aware of these differences when planning therapeutic interventions. The aging process is associated with multiple anatomical and physiological alterations in the cardiovascular system that can influence blood pressure regulation. Hypertension in young patients tends to be characterized by a hyperkinetic circulatory state, evidently resulting from increased sensitivity to circulating catecholamines (2). This state is expressed as an increase in heart rate, contractility, and cardiac output with no significant change in systemic vascular resistance. In contrast, systemic hypertension that is seen in elderly patients appears to be a consequence of structural vascular changes. A decreased vascular compliance and an increased resistance predominate and are associated with the narrowing of the vascular radius and increases in the vessel wall-to-lumen ratios (3). Histologically, the changes are apparent in the vascular subendothelial and media layers, which thicken with age and demonstrate increased connective tissue infiltration as well as calcification and lipid deposition (4). With age, this process results in a progressive increase in wall stiffness and tortuosity of the aorta and large arteries, often reflected by a rise in systolic pressure and a wide pulse pressure (5). The decreased vascular compliance seen in elderly patients may also result in reduced sensitivity of volume and baroreceptor function.
Aging also affects the vascular endothelium, the cells of which become smaller and less uniformly aligned. This change may result in a decreased production of endogenous vasodilating substances (e.g., nitric oxide) and a decline in the local control of vascular tone (6,7).

The aging process also alters the myocardium of elderly hypertensive patients. Although total heart size generally remains unchanged, mild to moderate left ventricular hypertrophy (LVH) often develops in response to an increased afterload. This hypertrophy tends to offset the decline in myocardial contractile speed and strength seen with aging (8). The elderly heart demonstrates microscopic foci of calcification and fibrosis as well as macroscopic calcification of the mitral and aortic valves and conduction system (9,10). Thus, the stiffened and hypertrophied left ventricle shows decreased diastolic filling and greater dependence on atrial contraction.

Renal function also shows an age-dependent decline, which is further accelerated by chronically elevated blood pressure. The decline in renal function often manifests as a decline in glomerular filtration rate (11). Postglomerular increases in vascular resistance have been described as a possible compensatory mechanism and may further increase vascular pressure in the glomerulus (12).

Despite the fact that elderly patients (including those with hypertension) tend to have lower plasma volumes than younger patients, their plasma renin levels are usually normal or low (13). Plasma levels of angiotensin-II, natriuretic peptides, and aldosterone are also decreased, and the response to antidiuretic hormone is blunted. In theory, these hormonal changes should help to lower or maintain arterial pressure in the elderly. Nonetheless, arterial blood pressure (usually systolic) appears to rise progressively with age (14–16).

It has been estimated that 80% of elderly hypertensive patients present with concomitant medical conditions, which must be taken into consideration while planning therapeutic intervention (17). Examples include coronary artery disease, diastolic and systolic dysfunction, diabetes mellitus, hyperlipidemia, renal impairment, and chronic obstructive pulmonary disease. Elderly patients often take nonsteroidal anti-inflammatory drugs for arthritic conditions, which can cause an increase in blood pressure. Elderly patients also frequently suffer from LVH, insulin resistance, obesity, mental depression, and cognitive dysfunction. Therapy for hypertensive elderly patients needs to account for these and other concomitant diseases.

**RATIONALE FOR TREATMENT**

It has been estimated that 50–70% of elderly Americans have systemic hypertension, which is defined by the National Institutes of Health as blood pressure greater than 140/90 mmHg (1,18). Higher levels of either systolic or diastolic blood pressure are associated with an increased risk of cardiovascular morbidity or mortality that include cases of coronary artery disease, congestive heart failure, renal insufficiency, peripheral vascular disease, and stroke. Hypertension in the elderly poses an important problem for two reasons: (1) the proportion of elderly in the population is steadily increasing and (2) the incidence of hypertension—and therefore the risk of cardiovascular disease—increases with age (19). In the past, there was a tendency to de-emphasize the clinical significance of elevated blood pressure readings in the elderly and to downplay the need for therapeutic interventions. Increasing blood pressure was viewed as part of the normal aging process, and levels of blood pressure that would dictate treatment in young adults were often considered satisfactory or borderline in elderly patients. It was believed that
the benefits of antihypertensive therapy might not be realized in patients with a limited life expectancy. It was also thought that elderly patients would be more susceptible to adverse drug reactions (e.g., orthostatic hypotension, cerebral hypoperfusion) (12,20).

Several large, randomized, well-controlled trials were designed to investigate whether elderly hypertensives respond positively and receive benefits from pharmacological intervention (Table 1). Examples include the European Working Party Study on High Blood Pressure in the Elderly (EWPHE), the Swedish Trial in Old Patients with Hypertension (STOP), the Medical Research Council Trial on Treatment of Hypertension in Older Adults (MRC II), and the Systolic Hypertension in the Elderly Program (SHEP) (21–25). The combined data reported from these trials demonstrated a reduction in both cerebrovascular and cardiovascular morbidity and mortality in treatment groups. A meta-analysis by Holzgreve (19) describes a 40% reduction in stroke incidence and a 30% reduction in cardiovascular events with antihypertensive therapy.

The SHEP study was particularly interesting because it investigated whether antihypertensive therapy can decrease cardiovascular risk in elderly patients with ISH (study entry criteria being systolic blood pressure 160–219 mmHg and diastolic pressure <90 mmHg), the most typical type of hypertension in the elderly (25). In the United States, the prevalence of diastolic hypertension tends to plateau around the age of 55, whereas the prevalence of systolic hypertension continues to rise, even after 80 years of age. Before the results of SHEP were published, many physicians held the belief that ISH in the elderly, reflecting an increase in rigidity of the arterial system, was only an index of an abnormal cardiovascular state and by itself did not play a direct role in the development of cardiovascular complications (26). This view persisted despite the compelling data from the Multiple Risk Factor Intervention Trial (MRFIT), which demonstrated that systolic blood pressure greater than 160 mmHg is a more significant risk factor, regardless of age, than diastolic pressure greater than 95 mmHg (27).

The results of the SHEP trial showed conclusively that reduction or correction of hypertension strongly diminished the risk. Antihypertensive therapy was associated not only with a decrease in the number of cerebrovascular events but also with a 25% reduction in fatal and nonfatal coronary events and an even greater benefit in reducing episodes of congestive heart failure (Table 2). The greatest benefit of therapy was seen in patients with severe underlying disease. Even patients over 80 years benefit from treatment (28,29). However, hypertension might not be a risk factor for cardiovascular disease among very old hypertensive patients with advanced atherosclerosis (30).

NONPHARMACOLOGICAL TREATMENT OF HYPERTENSION

Lifestyle modifications in the elderly may be the only treatment modality necessary for preventing and managing milder forms of hypertension (31). Reduction in excess body weight and mental stress, modification of alcohol intake, and increased physical activity can also reduce the doses of antihypertensive drugs used for blood pressure control. In the Trial of Nonpharmacologic Intervention in the Elderly (TONE), it was shown that the combination of dietary sodium restriction and regular moderate physical activity (30–45 min of brisk walking on most days) can prevent hypertension in older subjects, and help to control blood pressure in known hypertensives (32).

The Dietary Approaches to Stop Hypertension (DASH) trial showed that a diet rich in fruits and vegetables and low in saturated and total fat content can lower blood pressure without the need for additional drug treatment (33).
### Table 1  Characteristics of Some Long-Term Trials in Elderly Hypertensive Patients

<table>
<thead>
<tr>
<th>Study</th>
<th>Study Design</th>
<th>Number of Patient-years</th>
<th>Age (yr)</th>
<th>Males (yr)</th>
<th>Duration (yr)</th>
<th>BP at entry (mmHg)</th>
<th>BP Reduction* (mmHg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>EWPHE 1985</td>
<td>Randomized placebo-controlled double-blind</td>
<td>840</td>
<td>≥60</td>
<td>30</td>
<td>4.7</td>
<td>SBP 160–239</td>
<td>DBP 90–119</td>
</tr>
<tr>
<td>Coppe and Warrender 1986</td>
<td>Randomized non-blind</td>
<td>884</td>
<td>60–79</td>
<td>31</td>
<td>4.4</td>
<td>SBP ≥170</td>
<td>DBP ≥105</td>
</tr>
<tr>
<td>STOP 1991</td>
<td>Randomized placebo-controlled double-blind</td>
<td>1627</td>
<td>70–84</td>
<td>37</td>
<td>2.1</td>
<td>SBP 180–230</td>
<td>DBP 90–120</td>
</tr>
<tr>
<td>SHEP 1991</td>
<td>Randomized placebo-controlled single-blind</td>
<td>4736</td>
<td>≥60</td>
<td>43</td>
<td>4.5</td>
<td>SBP 160–219</td>
<td>DBP &lt;90</td>
</tr>
<tr>
<td>MRC Working Group</td>
<td>Randomized placebo-controlled single-blind</td>
<td>4396</td>
<td>65–74</td>
<td>39</td>
<td>5.8</td>
<td>SBP 160–209</td>
<td>DBP &lt;115</td>
</tr>
</tbody>
</table>

* Differences between blood pressure in control and active treatment groups.

**Abbreviations**: BP, blood pressure; SBP, systolic blood pressure; DBP, diastolic blood pressure; EWPHE, European Working Party Study on High Blood Pressure in the Elderly; STOP, Swedish Trial in Old Patients with Hypertension; SHEP, Systolic Hypertension in the Elderly Program; MRC, Medical Research Trial on Treatment of Hypertension in Older Adults.

**Source**: From Ref. 19.
Elderly patients with hypertension should be vigorously screened and treated for any additional cardiovascular risk factors that might be present, including cigarette smoking, hypercholesterolemia, diabetes mellitus, and excessive alcohol intake.

**PHARMACOLOGICAL TREATMENT OF HYPERTENSION**

**Diuretics**

Diuretics such as hydrochlorothiazide (HCTZ) and chlorthalidone have been the mainstay of antihypertensive drug treatment in the elderly for over 40 years. The Seventh Joint National Committee (JNC 7) report recommends diuretics as a medication of choice for initiating drug therapy of hypertension (1). Diuretic use will cause an initial reduction in intravascular volume, and will lower peripheral vascular resistance (34–36). These drugs will reduce an elevated blood pressure in over 50% of patients, and they are well tolerated and relatively inexpensive. Several clinical trials have assessed the efficacy of diuretics in hypertension and their ability to also reduce the complications of hypertension in the elderly, especially cardiovascular, cerebrovascular, and renal diseases.

The EWPHE trial was a double-blinded, randomized, placebo-controlled study that evaluated 840 patients above 60 years of age with blood pressure ranging from 160 to 239 mmHg/90 to 119 mmHg (22). The subjects received, in an increasing stepwise fashion, HCTZ 25 to 50 mg and triamterene 50 to 100 mg to achieve blood pressure control or placebo. Methyldopa 500 mg was added if the blood pressure remained elevated. The subjects were followed for seven years and the outcomes of cardiovascular mortality and all-cause mortality were reported on. With active treatment, blood pressure was lowered by 19 mmHg/5 mmHg compared with placebo with less than 35% requiring the addition of methyldopa. It was found that 29 fewer cardiovascular events occurred per 1000 patient-years and 14 fewer deaths per 1000 patient-years, which was about a 38% decrease in total cardiovascular death compared with placebo.

The National Heart Foundation of Australia studied 582 patients aged 60 to 69 years with diastolic blood pressures of 95 to 110 mmHg and started them on chlorothiazide 500 to 1000 mg to obtain blood pressure control or placebo (37). If blood pressure did not reach goal levels, a β blocker or methyldopa was added. Subsequently, hydralazine or clonidine was given, if necessary. Patients were followed for over five years, looking at the endpoints of fatal and nonfatal cardiovascular events. Seventy percent of the actively

<table>
<thead>
<tr>
<th>Table 2 Five-Year Absolute Benefits Found in Placebo-Controlled Endpoint Studies in ISH</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of events prevented/1000 patients*</td>
</tr>
<tr>
<td>SHEP (25)</td>
</tr>
<tr>
<td>Stroke events</td>
</tr>
<tr>
<td>Major CV events</td>
</tr>
<tr>
<td>Deaths</td>
</tr>
<tr>
<td>Dementia</td>
</tr>
</tbody>
</table>

*With the therapy/regimen used in this study.

**Abbreviations:** ISH, isolated systolic hypertension; SHEP, Systolic Hypertension in the Elderly Program; Syst-Eur, Systolic Hypertension in Europe; Syst-China, Systolic Hypertension in China.

**Source:** From Ref. 109.
treated patients had diastolic blood pressure less than 90 mmHg, and of those actively
treated, only 15% required more than two drugs. Most importantly, there was a decrease
of 38% in total fatal and nonfatal cardiovascular events with active treatment compared
with placebo.

A third multicenter, randomized, double-blind, placebo-controlled trial, SHEP,
looked at 4736 patients older than 60 years with systolic blood pressure 160 to 219 mmHg
and diastolic pressures less than 90 mmHg (ISH) (25). Patients were started on placebo or
chlorthalidone 12.5 mg, and the dose was doubled if the systolic blood pressure goal was
not achieved. If at subsequent visits the blood pressure goal was not attained, then
atenolol 25 to 50 mg was added. If atenolol was contraindicated, reserpine was given.
After five years of treatment, the actively treated group had a reduced incidence of stroke,
myocardial infarction (MI), and heart failure. Further analyses of the data show that the
development of fatal and nonfatal heart failure was 55 of 2365 in the actively treated
group compared with 105 of 2371 in the placebo group (38). Additionally, there were 583
non-insulin-dependent diabetics at baseline and their absolute risk reduction was twice as
great in developing cardiovascular events (39).

A randomized, single-blinded, placebo-controlled trial done by the MRC studied
4396 patients aged 65 to 74 years with a systolic blood pressure of 160 to 209 mmHg
and a diastolic blood pressure less than 115 mmHg. The subjects received HCTZ 25 to 50 mg
plus amiloride 2.5 to 5 mg, atenolol 50 to 100 mg, or placebo, and were followed for five
years for incidence of stroke and coronary events as well as for all cardiovascular events
(24). The results showed that both active treatments reduced blood pressure and the
incidence of stroke equally, but the diuretic group experienced a more rapid and greater
control of blood pressure compared with the β-blocker group, especially within the first
three months of treatment, and the patients on the HCTZ regimen had 44% fewer
 coronary events and 29% fewer cardiovascular events than the atenolol treatment
group.

More recently, the Antihypertensive and Lipid-Lowering Treatment to Prevent
Heart Attack Trial (ALLHAT) studied 33,357 patients with a mean age of 67 who had
stage I or II hypertension and at least one risk factor for coronary heart disease, and
looked at fatal and nonfatal coronary heart disease or MI, stroke, and all coronary
and cardiovascular events (40). Patients were randomized to receive chlorthalidone 12.5 to
25 mg, amlodipine 2.5 to 10 mg or lisinopril 10 to 40 mg, and followed for five years.
If blood pressure goal was not achieved, step 2 drugs were added: atenolol 25 to 100 mg,
reserpine 0.05 to 0.2 mg, clonidine 0.1 to 0.3 mg, twice a day. If necessary, step
3 treatment with hydralazine 25 to 100 mg, twice a day, was added. All treatment groups
showed a similar decrease in the number of fatal and nonfatal coronary heart disease
events. All treatments reduced blood pressure effectively, but the systolic blood pressure
was lower in the diuretic group, and the lisinopril group had a 15% higher risk of stroke, a
10% higher risk of cardiovascular disease, and a 19% higher risk of heart failure
compared with the chlorthalidone group. Furthermore, the amlodipine group had a 38%
higher rate of heart failure when compared with the chlorthalidone group. Given the data
from all these studies, it is reasonable to start antihypertensive therapy with diuretic
agents in the elderly unless there are concomitant conditions present, such as angina
pectoris or diabetes mellitus, which might warrant treatment with other agents.

Why Not Use a Diuretic?
As mentioned earlier, with aging, physiological changes occur that can be exacerbated
with diuretic use. The elderly typically have contracted intravascular volumes and
Impaired baroreflexes, and diuretics cause sodium and water depletion (hypovolemia) and orthostatic hypotension. Older people have a high prevalence of LVH, which predisposes to ventricular ectopy and sudden death. Diuretics can cause hypokalemia and hypomagnesemia, which can increase ventricular ectopy and other arrhythmias. Typically, hypokalemia and hypomagnesemia can develop in the first few days of treatment. However, after that the body can achieve a new homeostatic balance and loss of these ions is lessened. Nevertheless, these agents are not advised in patients with baseline abnormalities, and when using them, potassium levels should be monitored and supplementation should be given as needed (41). Also, as we age, there is a lower renal blood flow and glomerular filtration rate. Diuretic use can cause a decrease in renal blood flow, creatinine clearance, and glomerular filtration rate. The elderly have a tendency toward hyperuricemia and glucose intolerance. Diuretics can cause increases in uric acid and glucose intolerance. Diuretic use can cause dyslipidemia. Cholesterol levels have been shown to increase in the first year of treatment with thiazides (42). However, their long-term use has been associated with an overall decrease in baseline cholesterol levels. Of the clinical trials mentioned, about 160 patients withdrew from the MRC trial because of side effects (less than the \( \beta \)-blocker group) and 15% withdrew from the ALLHAT trial because of side effects all comparable to the other treatment groups. In the SHEP trial, the most frequent event observed was abnormal electrolyte levels.

Hypokalemia can be avoided when using an aldosterone antagonist diuretic such as spironolactone, triamterene, or eplerenone with a thiazide. Caution should be taken when using aldosterone inhibitors in patients with renal dysfunction. There may also be a greater blood pressure lowering effect with the combination than that seen with either diuretic drug used alone without the need for potassium supplementation. Eplerenone has been shown to reduce mortality in survivors of MI with evidence of left ventricular dysfunction (43).

**\( \beta \)-Adrenergic Blockers**

Although \( \beta \) blockers have been used for the treatment of hypertension in the elderly for several years, evidence of their benefit has not been convincing. The major studies of their efficacy, safety, and tolerability for the treatment of elderly hypertensives include the MRC, STOP, STOP-2, SHEP, and LIFE (Losartan Intervention for Endpoint Reduction in Hypertension Study) trials.

The MRC trial assessed whether treatment with a diuretic or a \( \beta \) blocker in hypertensive older adults reduced the risk of stroke, coronary artery disease, and death (24). As described earlier, both treatments reduced blood pressure below the level of the placebo group, but only diuretic therapy showed a significant reduction in stroke, coronary events, and all cardiovascular events. The \( \beta \)-blocker group showed no significant reductions in these endpoints from placebo. Another significant finding of this trial was poor tolerability of \( \beta \) blockers, which is illustrated by the dropout rate of 63% of patients randomized to receive atenolol (24).

The STOP trial was a multicenter, randomized, double-blind trial in subjects aged 70 to 84 years with systolic blood pressures ranging from 180 to 230 mmHg and/or diastolic blood pressure of 105 to 120 mmHg (23). Patients were initially treated with either a \( \beta \) blocker or a diuretic. However, two-thirds of the active subjects received combination therapy. The primary endpoints of stroke, MI, and cardiovascular death were reduced by active treatment compared with placebo. A separate report described no differences in monotherapy for diastolic blood pressure reduction during the first two months, but diuretics were more effective for systolic blood pressure reduction in...
the first two months of the trial (44). The β blockers included in the trial were 100 mg metoprolol controlled-release once daily, 50 mg atenolol once daily, or 5 mg pindolol once daily. At 12 months, the placebo-corrected changes in blood pressure were greatest when the β blocker was combined with a diuretic. There were no data collected in this trial to suggest either a benefit or a risk of β-blocker treatment in terms of mortality.

STOP-2, a prospective, randomized, open-blinded endpoint design trial evaluated 6614 patients aged 70 to 84 years with systolic blood pressure greater than or equal to 180 mmHg and diastolic blood pressure greater than or equal to 105 mmHg, or both (45). Patients were assigned to receive either an angiotensin-converting enzyme (ACE) inhibitor, a calcium antagonist, or conventional drug therapy with a β blocker or a diuretic or a combination of both. There was no difference in the proportion of patients reaching a primary endpoint in this trial. Conventional therapy was just as effective as the newer agents in reducing cardiovascular events. Again, there were no findings in this trial to suggest either a benefit or risk from β-blocker treatment.

As mentioned in the diuretics section of this chapter, the SHEP trial was a multicenter, randomized, double-blind, placebo-controlled trial of persons aged 60 years or older (25). Initial therapy was with 12.5 to 25 mg of chlorthalidone once daily. If blood pressure was not controlled, then 25 to 50 mg of atenolol or 0.05 mg of reserpine was added once daily. Forty-four percent of the subjects required combination drug therapy to achieve blood pressure control. This was a diuretic-based trial, and not a study of β blockers. A post hoc analysis suggested that neither the β blocker nor reserpine added to the benefits observed in this trial.

The LIFE study was a double-blind, randomized, parallel group trial of 9193 participants aged 55 to 80 years, with essential hypertension and LVH ascertained by ECG (46). Participants were assigned to once-daily losartan-based or atenolol-based antihypertensive treatment for at least four years. Although both regimens effectively reduced blood pressure, losartan proved to be more effective than atenolol in preventing cardiovascular morbidity and mortality for a similar reduction in blood pressure. Losartan was also better tolerated, since more patients on β blockers withdrew because of the side effects of therapy.

Messerli et al. published a meta-analysis of 10 studies comparing β blockers and diuretics for the treatment of hypertension in the elderly (47). A total of 16,154 patients aged 60 years and older were included. Two-thirds of the patients assigned to diuretics were well controlled on monotherapy. Diuretic therapy was superior to β blockade with regard to all clinical endpoints, and was more effective in preventing cerebrovascular events, fatal stroke, coronary artery disease, cardiovascular mortality, and all-cause mortality.

Therefore, the clinical benefits of β blockers as monotherapy in the treatment of systemic hypertension in the elderly are poorly documented, although they may have a role in combination therapy, especially with diuretics. β Blockers have an established role in the treatment of certain arrhythmias, migraine headaches, senile tremor, coronary artery disease, and congestive heart failure. Consideration should be given to adding β blockers as a treatment regimen in hypertensive patients with any of these comorbid conditions (48–52). It was shown that in older patients with ISH, a clinical heart rate greater than 79 bpm was a significant predictor for an increase in all-cause, cardiovascular, and noncardiovascular mortality, suggesting a role for β blockers and rate-lowering calcium blockers in this population (53).

β Blockers, especially nonselective β blockers, should be used carefully in patients with asthma and chronic obstructive pulmonary disease, since they can induce bronchospasm by inhibiting sympathetic signaling at the β2-adrenergic receptors (48).
As glucose metabolism is modulated by the sympathetic nervous system, β blockers can exacerbate diabetes mellitus by inhibiting this pathway. Although a deterioration in glucose tolerance has been associated with nonselective agents such as propranolol, this finding has not been as frequently observed with β1-selective agents such as metoprolol and atenolol (48). Also, β blockers can mask the sympathetic manifestations of hypoglycemia. These probably do not increase the risk of depression, but they can cause erectile dysfunction (48). Viagra® can be used with concomitant antihypertensive drugs to alleviate erectile dysfunction.

**Calcium Blockers**

The calcium channel blockers are a heterogeneous group of drugs with widely variable effects on heart muscle, sinus node function, atrioventricular conduction, peripheral blood vessels, and coronary circulation (54–57). From a chemical standpoint, they can be divided into three main groups: phenylalkylamines (verapamil), benzothiazepines (diltiazem), and dihydropyridines (nifedipine, nicardipine, nimodipine, amlodipine, felodipine, isradipine). Despite their heterogeneity, they all block the influx of calcium ions into the cells of vascular smooth muscle and myocardial tissue (58).

The observation that calcium antagonists are significantly more effective in inhibiting contraction in coronary and peripheral arterial smooth muscle than in cardiac and skeletal muscle is of great clinical importance. This differential effect is explained by the observation that arterial smooth muscle is more dependent on external calcium entry for contraction, whereas cardiac and skeletal muscle rely on a recirculating internal pool of calcium (59). Because calcium antagonists are membrane-active drugs, they reduce the entry of calcium into cells and, therefore, exert a much greater effect on vascular wall contraction. This preferential effect allows calcium antagonists to dilate coronary and peripheral arteries in doses that do not severely affect myocardial contractility or have little, if any, effect on skeletal muscle (54).

Based on the above mechanisms of action, the calcium antagonists appear well suited for use in elderly patients whose hypertensive profile is based on increasing arterial stiffness, decreased vascular compliance, and diastolic dysfunction secondary to atrial and ventricular stiffness (60). Because they have multiple clinical applications, including treatment of angina pectoris and management of supraventricular arrhythmias, calcium antagonists also hold promise in the treatment of elderly hypertensive patients with comorbid cardiovascular conditions.

In general, calcium antagonists appear to be well tolerated by the elderly. Most adverse effects of the dihydropyridines are attributable to vasodilation; examples include headaches and postural hypotension. Postural hypotension is associated with an increased risk of dizziness and falls; thus, it is a serious concern for elderly patients. Peripheral edema may also result and be confused with symptomatic congestive heart failure (61). Verapamil, which may be particularly useful in elderly patients with diastolic dysfunction of the left ventricle, has been noted to increase constipation (62). Verapamil and diltiazem can precipitate heart blocks in elderly patients with underlying conduction defects. Age-related declines in renal or hepatic function alter drug disposition in elderly patients, mostly as a result of declines in first-pass metabolism. This decline decreases total body clearance and increases elimination half-life. Individualized dose adjustments or dosing schedules help to decrease adverse effects (63).

The published results of large double-blind, randomized, placebo- and active-controlled trials have demonstrated the safety and efficacy of calcium antagonists in elderly patients with both ISH and combined systolic and diastolic hypertension (Table 3).
### Table 3  Trials of Antihypertensive Therapy with Calcium Antagonists in Elderly Patients

<table>
<thead>
<tr>
<th>Trial</th>
<th>Duration</th>
<th>Number of patients</th>
<th>Entry criteria</th>
<th>Therapy</th>
<th>Endpoints</th>
</tr>
</thead>
<tbody>
<tr>
<td>ALLHAT</td>
<td>5 yr</td>
<td>40,000</td>
<td>Age &gt;55 yr&lt;br&gt;BP: 140/90 or lower if treated&lt;br&gt;Other</td>
<td>1st: amlodipine, lisinopril, doxazosin, or chlorthalidone + pravastatin&lt;br&gt;2nd: reserpine, clonidine, atenolol, or hydralazine at physician’s discretion</td>
<td>1st: fatal/nonfatal MI&lt;br&gt;2nd: morbidity, mortality, cost, benefits of cholesterol reduction</td>
</tr>
<tr>
<td>CONVINCE</td>
<td>5 yr</td>
<td>15,000</td>
<td>Age ≥55 yrs&lt;br&gt;BP: systolic 140–190 or diastolic 90–100 or 175–100 if treated&lt;br&gt;Other</td>
<td>1st: verapamil, atenolol, or HCTZ&lt;br&gt;2nd: HCTZ or β blocker for achievement of BP goal&lt;br&gt;3rd: moexipril</td>
<td>1st: fatal/nonfatal MI&lt;br&gt;stroke; sudden cardiac death&lt;br&gt;2nd: cardiovascular disease, number and time of deaths</td>
</tr>
<tr>
<td>HOT</td>
<td>2.5 yr</td>
<td>18,000</td>
<td>Age 50–80 yr&lt;br&gt;BP: diastolic 100–115</td>
<td>1st: felodipine + aspirin or placebo&lt;br&gt;2nd: captopril, enalapril, ramipril, atenolol, metoprolol, or propranolol, as needed</td>
<td>1st: fatal/nonfatal MI&lt;br&gt;stroke; achievement of BP goal&lt;br&gt;2nd: benefits of aspirin</td>
</tr>
<tr>
<td>INSIGHT</td>
<td>3 yr</td>
<td>6321</td>
<td>Age 55–80 yr&lt;br&gt;BP ≥ 150/95 (sitting) or systolic &gt; 160&lt;br&gt;Other</td>
<td>1st: long-acting nifedipine or HCTZ-amiloride&lt;br&gt;2nd: atenolol or enalapril</td>
<td>1st: fatal/nonfatal MI&lt;br&gt;stroke; congestive heart failure&lt;br&gt;2nd: mortality</td>
</tr>
<tr>
<td>NORDIL</td>
<td>5 yr</td>
<td>10,881</td>
<td>Age 50–74 yr&lt;br&gt;BP: diastolic &gt;110 or &gt;100 (sitting) if treated or other risk factors present</td>
<td>1st: diltiazem, diuretic, or beta blocker&lt;br&gt;2nd: ACE inhibitor, β blocker, or diuretic&lt;br&gt;3rd: ACE inhibitor, β blocker, or diuretic</td>
<td>1st: fatal/nonfatal MI&lt;br&gt;stroke; sudden cardiac death&lt;br&gt;2nd: mortality, ischemia heart disease or attack, atrial fibrillation, congestive heart failure, renal disease&lt;br&gt;1st: fatal/nonfatal cardiovascular disease</td>
</tr>
<tr>
<td>PREDICT</td>
<td>4–4.5 yr</td>
<td>8000–8500</td>
<td>Age ≥55 yr&lt;br&gt;BP: 90–109/140–179&lt;br&gt;Other</td>
<td>1st: diltiazem or chlorthalidone&lt;br&gt;2nd: open-label therapy&lt;br&gt;3rd: open-label therapy</td>
<td>1st: compare effects on EKG measurements of ventricular wall thickness and ventricular function&lt;br&gt;1st: fatal/nonfatal MI&lt;br&gt;stroke; sudden cardiac arrest&lt;br&gt;2nd: cardiovascular disease, cost, institutionalization, tolerability of therapy</td>
</tr>
<tr>
<td>SISH</td>
<td>2 yr</td>
<td>171</td>
<td>Age &gt;55 yr&lt;br&gt;BP: systolic 140–159</td>
<td>1st: felodipine or placebo&lt;br&gt;3rd: open-label therapy</td>
<td>1st: compare effects on EKG measurements of ventricular wall thickness and ventricular function&lt;br&gt;1st: fatal/nonfatal MI&lt;br&gt;stroke; sudden cardiac arrest&lt;br&gt;2nd: cardiovascular disease, cost, institutionalization, tolerability of therapy</td>
</tr>
<tr>
<td>STOP-2</td>
<td>4 yr</td>
<td>6600</td>
<td>Age 70–84 yr&lt;br&gt;BP&gt;180/105 (sitting)</td>
<td>1st: felodipine, isradipine, atenolol, metoprolol, pindolol, enalapril, lisinopril, or HCTZ-amiloride</td>
<td>1st: fatal/nonfatal MI&lt;br&gt;stroke; sudden cardiac arrest&lt;br&gt;2nd: cardiovascular disease, cost, institutionalization, tolerability of therapy</td>
</tr>
</tbody>
</table>
Three studies have evaluated two dihydropyridines, long-acting nitrendipine, and felodipine in patients with ISH. The Systolic Hypertension in Europe (SYST-EUR) study was limited to patients aged 60 years and older with a resting systolic pressure of 160 to 219 mmHg, and a diastolic pressure less than 95 mmHg. Patients were randomized to receive nitrendipine or placebo. If additional blood pressure control was necessary, patients received an ACE inhibitor and then a diuretic. Compared with placebo, nitrendipine therapy was associated with significant reductions in the rate of stroke, major cardiovascular events, and cognitive disorders (64–66). On the basis of this study, the JNC-7 guidelines include the use of dihydropyridine calcium antagonists in addition to thiazide diuretics as first-line treatment for ISH in the elderly (1).

The Systolic Hypertension in China (SYST-CHINA) study also looked at nitrendipine as a first-line treatment modality compared with placebo in elderly patients with ISH (67). Compared with placebo, nitrendipine was associated with a reduction in stroke events, major cardiovascular events, and mortality.

The stage I Systolic Hypertension in the Elderly (68) was a pilot trial that enrolled elderly patients (>55 years of age) with mild (stage 1) systolic hypertension (140 to 155 mmHg), a population not studied in SHEP, SYST-EUR, and SYST-CHINA. Felodipine was compared with placebo in an attempt to reduce systolic blood pressure by 10%. Felodipine was shown to be more effective than placebo in reducing blood pressure. In addition, the drug was shown to reduce ventricular wall thickness and improved ventricular function (68,69).

A number of studies have been completed comparing various calcium blockers to other antihypertensive drugs in older subjects with combined systolic and diastolic hypertension (Table 3). STOP-2 enrolled 6600 patients, ranging in age from 70 to 84 years with a supine blood pressure of 180/105 mmHg or higher (45). The original STOP

Table 3: Trials of Antihypertensive Therapy with Calcium Antagonists in Elderly Patients

<table>
<thead>
<tr>
<th>Trial</th>
<th>Duration</th>
<th>Number of patients</th>
<th>Entry criteria</th>
<th>Therapy</th>
<th>Endpoints</th>
</tr>
</thead>
<tbody>
<tr>
<td>Syst-Eur 5 yr</td>
<td>3000</td>
<td>Age ≥ 60 yr</td>
<td>BP: systolic 160–219 or diastolic &lt; 95 (sitting)</td>
<td>1st: nitrendipine or placebo 2nd: enalapril, HCTZ</td>
<td>1st: fatal/nonfatal stroke 2nd: MI, congestive failure</td>
</tr>
<tr>
<td>Syst-China</td>
<td>Same as Syst-Eur</td>
<td>1st: nitrendipine or placebo 2nd: captopril, HCTZ, or placebo</td>
<td>1st &amp; 2nd same as Syst-Eur</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Abbreviations: BP, blood pressure (mmHg); MI, myocardial infarction; EKG, electrocardiographic; HCTZ, hydrochlorothiazide; ACE, angiotensin-converting enzyme; ALLHAT, Antihypertensive and Lipid-lowering Treatment to Prevent Heart Attack Trial; CONVINCE, Controlled Onset Verapamil Investigation of Cardiovascular Endpoints; HOT, Hypertension Optimal Treatment Study; INSIGHT, International Nifedipine Study: Intervention as a Goal in Hypertension Treatment; NORDIL, Norwegian Diltiazem Intervention Study; PREDICT, Prospective Randomized Evaluation of Diltiazem CD Trial; SISH, Stage 1 Systolic Hypertension; STOP-2, Swedish Trial in Old Patients with Hypertension 2; Syst-Eur, Systolic Hypertension in Europeans Study; Syst-China, Systolic Hypertension in China.

Source: From Ref. 110.
trial (23) compared the effects of diuretics and β blockers in elderly hypertensives in terms of cardiovascular morbidity and mortality. STOP-2 (45) compared these two treatments with a calcium blocker (felodipine or isradipine) or an ACE inhibitor (enalapril or lisinopril). There was no difference between the three treatment groups with respect to the combined endpoints of fatal stroke, fatal MI, and other cardiovascular diseases (45,70). There was a lower incidence of nonfatal MI and congestive heart failure in the ACE inhibition group compared with the other treatment modalities. In the International Nifedipine Study Intervention as a Goal in Hypertension Treatment (INSIGHT) (71), 6321 elderly patients aged 55 to 80 years were randomized to double-blind treatment with either long-acting nifedipine gastrointestinal therapeutic system (GITS) or the combination drug coamilozide (HCTZ and amiloride). The study endpoints were overall cardiovascular morbidity and mortality, and both treatments appeared equally effective in preventing vascular events. In the Nordic Diltiazem Study (NORDIL) (72), 10,881 patients aged 50 to 74 years with systemic hypertension were randomized to receive first-line therapy with diltiazem, diuretics, or β blockers. Diltiazem was as effective as the other treatments in reducing the incidence of combined study endpoints of stroke, MI, and other cardiovascular deaths. In the Prospective Randomized Evaluation of Diltiazem CD Trial (PREDICT) study, 8000 patients aged 55 years and older were randomized to receive either diltiazem or chlorthalidone. The results have not been published to date. Other studies have demonstrated the efficacy of calcium-channel blockers used alone or in combination in elderly patients when compared to alternative medications (73–77).

The Hypertension Optimal Treatment (HOT) trial studied 18,000 patients aged 50 to 80 years. The study examined whether maximal reduction of diastolic blood pressure with antihypertensive drugs and aspirin could cause a further reduction in cardiovascular events (MI or stroke) or be associated with harm (J-curve hypothesis) (78). Felodipine, a long-acting dihydropyridine, was used as the first-line treatment for all patients and aspirin (75 mg) or placebo was also given. An ACE inhibitor, a β blocker, and a thiazide diuretic could be given to achieve the desired diastolic blood pressure goal. The study results showed that maximal protection with antihypertensive therapy was seen when a diastolic blood pressure of 82.6 mmHg was achieved; in diabetic patients, an additional reduction in diastolic blood pressure (below 80 mmHg) was needed to achieve maximal benefit. A J-curve response was not observed despite major reductions in blood pressure. The HOT study had greater success in achieving blood pressure targets among the oldest subjects with a low incidence of medication side effects.

The Controlled-Onset Verapamil Investigation of Cardiovascular Events trial (CONVINCE) (79) (Table 3) was designed to compare a delayed slow-release verapamil delivery system with atenolol or HCTZ in 15,000 hypertensive patients aged 55 years and older. The sponsor stopped the study for financial reasons, and the accumulated data from the trial showed no difference in the clinical endpoints with either treatment regimen. Calcium antagonists are well suited for treating elderly hypertensive patients who often have concomitant diseases, especially coronary artery disease or heart failure due to diastolic dysfunction (Table 4). In an elderly patient with both hypertension and ischemic heart disease (with or without angina pectoris), calcium antagonists are an appropriate therapy for both conditions (80). The combination of a calcium antagonist and a β blocker is well tolerated and serves to offset transient increases in the neurohumoral reflex (81). A combination regimen of felodipine and metoprolol has been evaluated, but this formulation is not yet available for clinical use in the United States (82). Combinations of calcium blockers with ACE inhibitors have also been evaluated (83). The edema seen with the calcium blocker is reduced, while there is greater blood pressure efficacy with
<table>
<thead>
<tr>
<th>Cardiovascular disease</th>
<th>General population (%)</th>
<th>Trial participants (%) (age &gt; 60 yr)</th>
<th>Elderly Patients with hypertension (%) (age &gt; 65 yr)</th>
<th>Residents of nursing homes (%) (age 65–74 yr)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Men</td>
<td>Women</td>
<td>SHEP</td>
<td>Syst-Eur</td>
</tr>
<tr>
<td>Angina</td>
<td>14.7</td>
<td>8.6</td>
<td>4.9</td>
<td>8.8</td>
</tr>
<tr>
<td>MI</td>
<td>11.1</td>
<td>4.4</td>
<td>—</td>
<td>3.5</td>
</tr>
<tr>
<td>CHF</td>
<td>2.0</td>
<td>1.3</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>Stroke</td>
<td>3.5</td>
<td>1.3</td>
<td>1.4</td>
<td>1.2</td>
</tr>
<tr>
<td>Diabetes</td>
<td>22.9</td>
<td>20.1</td>
<td>10.1</td>
<td>10.5</td>
</tr>
<tr>
<td>Dementia</td>
<td>—</td>
<td>—</td>
<td>0.4</td>
<td>0.8</td>
</tr>
<tr>
<td>Depression</td>
<td>—</td>
<td>—</td>
<td>11.1</td>
<td>—</td>
</tr>
</tbody>
</table>

**Abbreviations:** MI, myocardial infarction; CHF, congestive heart failure; SHEP, Systolic Hypertension in the Elderly Program; Syst-Eur, Systolic Hypertension in Europe; Syst-China, Systolic Hypertension in the Elderly Chinese; —, data not available.

**Source:** From Ref. 111.
combination therapy than with monotherapy. Recently a combination of amlodipine and valsartan was approved for clinical use in hypertension.

Elderly patients with diastolic dysfunction have impaired myocardial relaxation, which leads to decreased ventricular filling. Impairment may be related to age or to myocardial ischemia from coronary disease (84). Calcium antagonists may help to improve left ventricular diastolic function in such patients (85).

ACE Inhibitors

ACE inhibitors block the conversion of angiotensin-I to angiotensin-II both systemically and locally in arterioles to lower total peripheral vascular resistance. Blood pressure is reduced without reflex stimulation of heart rate and cardiac output. With age, angiotensin levels become lower and, theoretically, ACE inhibitors should not be as effective as other therapies. However, multiple studies have shown otherwise.

The Captopril Prevention Project (CAPPP) compared captopril with a β blocker in 10,925 older patients with diastolic blood pressure greater than 100 mmHg (86). Patients receiving captopril had a lower rate of cardiovascular death; patients on β blockers had a lower stroke rate. Other studies mentioned earlier (ALLHAT and STOP-2) (40,45) showed that ACE inhibitors can reduce the risk of stroke and coronary heart disease as well as other antihypertensive drugs, although in ALLHAT there was less of a reduction, especially in Black patients.

ACE inhibitors have been shown to reduce the risk of recurrent stroke when combined with a diuretic in patients who have already had a stroke or transient ischemic attack (87). In addition, they have been shown to reduce mortality in patients with heart failure and poor left ventricular function (88–92). The drugs appear to reduce the progression of renal disease in type 1 diabetic patients with proteinuria (93).

The Heart Outcomes Prevention Evaluation (HOPE) trial evaluated the effects of ramipril in 9297 patients over the age of 55 who were both normotensive and hypertensive in a placebo-controlled trial (94). Subjects had a previous history of stroke, coronary disease, peripheral vascular disease, and diabetes mellitus without heart failure. After five years, the endpoints of MI, stroke, or cardiovascular death were evaluated. Ramipril was associated with a lower blood pressure than placebo, and reduced the risk of the combined primary outcome by 25%, MI by 22%, stroke by 33%, and cardiovascular death by 37%.

Given all the available data, ACE inhibitors should be considered as drugs of choice in elderly hypertensive patients with heart failure and/or diabetes mellitus. The main adverse effects of ACE inhibitors include excessive hypotension, chronic dry cough, and, rarely, angioedema or rash. Renal failure can develop in those with renal artery stenosis. Hyperkalemia can occur in patients with renal insufficiency or those taking potassium supplements. Therefore, these agents must be used carefully in patients with renal impairment. Rarely, neutropenia or agranulocytosis can occur; therefore, close monitoring is suggested in the first few months of therapy.

Angiotensin Receptor Blockers

The angiotensin receptor blockers (ARBs) are a relatively new class of drugs employed in the treatment of hypertension. These agents work selectively at the AT1-receptor subtype, the receptor that mediates all the known physiological effects of angiotensin-II that are believed to be relevant to cardiovascular and cardiorenal homeostasis.
A large-scale open-label clinical experience trial ACTION study showed the effectiveness of the ARB candesartan cilexetil alone or in combination with other agents in 6465 patients with a mean age of 58 who had either combined or ISH (95). The LIFE study compared losartan with atenolol in 9193 patients aged 55 to 80 years with essential hypertension and LVH (46). The study showed a substantially reduced rate of stroke in the losartan-treated group despite comparably reduced blood pressure reduction in both the losartan and atenolol treatment groups. A primary composite outcome of death, stroke, and cardiovascular mortality showed a significant benefit in favor of losartan. There was also a greater effect on LVH regression with losartan compared with atenolol.

Overall, safety and efficacy trials have shown that ARBs are similar to other agents in reducing blood pressure and are well tolerated. ARBs have also been found useful in protecting the kidney in the setting of type 2 diabetes (46), both in patients with established diabetic nephropathy with proteinuria and in patients with microalbuminuria (93). In addition, the drugs have been shown useful in reducing mortality and morbidity in patients with congestive heart failure (93,96), used alone and in combination with an ACE inhibitor (97).

In elderly patients, ARBs can be considered a first-line treatment in hypertensive patients with type 2 diabetes, and as an alternative to ACE inhibitors in hypertensive patients with heart failure who cannot tolerate ACE inhibition (96). In a study of patients with chronic heart failure and preserved left ventricular ejection fraction (>40%), candesartan was shown to reduce the number of hospital admissions for heart failure compared with placebo, but the active treatment had no impact on mortality (98).

\(\alpha\)-Adrenergic Blocking Agents

In large comparative clinical trials, the efficacy and safety of \(\alpha\) blockers have been well documented (48). Doxazosin 2 to 8 mg daily was one of the drugs used in the ALLHAT trial, and that arm of the study was discontinued after an interim analysis showed a 25% greater rate of cardiovascular events compared with chlorthalidone, largely driven by congestive heart failure (99). On the basis of this study, \(\alpha\) blockers should not be considered as first-line monotherapy treatment for hypertension, but as part of a combination regimen to provide maximal blood pressure control. These drugs are a treatment of choice for symptomatic prostate hypertrophy, and caution should always be used because of their potent hypotensive actions.

Direct Renin Inhibitors

Recently released for clinical use, aliskiren is the first orally active direct renin inhibitor approved for the treatment of systemic hypertension. In doses of 150 to 300 mg taken once daily, aliskiren can effectively lower blood pressure, and it was shown to be as effective as ARBs and ACE inhibitors for blood pressure management (100–102). Combining aliskiren with HCTZ, ramipril, or amlodipine causes greater blood pressure–lowering than with either agent used alone (100,103). There is no experience with combination of aliskiren and \(\beta\)-blocker therapy, or with maximal dose ACE inhibitors. There are also little data available in Black hypertensive patients (104).

Aliskiren has been studied in older patients (>75 years) and appears to be well tolerated with no dose adjustment necessary. In addition, there is no dose adjustment of aliskiren necessary in older patients with renal disease. The major dose-related side effect...
of aliskiren is a lower incidence of mild diarrhea, which in clinical studies did not lead to treatment discontinuation (105).

**Centrally Acting Agents**

Centrally acting agents (e.g., clonidine) are not first-line treatments in the elderly because many patients experience troublesome sedation. They can be used as part of a combination regimen to maximize blood pressure control.

**Combination Therapy**

Treating hypertension with combination therapy provides more opportunity for creative solutions to a number of problems. Five issues in combined therapy—some practical, some speculative—are listed in Table 5 (106).

The most obvious benefit of drug combinations is the enhanced efficacy that fosters their continued widespread use. Theoretically, some drug combinations might produce synergistic effects that are greater than would be predicted by summing the efficacies of the component drugs. More commonly, combination therapy achieves a little less than the sum of its component drug efficacies. In contrast, some combinations of drugs produce offsetting interactions that weaken rather than strengthen their antihypertensive effects, as previously seen with agents affecting peripheral-neuronal actions. For instance, guanethidine and reserpine produced this offsetting interaction; but since these agents are now used only rarely, this issue need not be considered further.

A second benefit of combination therapy concerns the avoidance of adverse effects. When patients are treated with two drugs, each drug can be administered in a lower dose that does not produce unwanted side effects but still contributes to overall efficacy. A third issue concerns convenience. Obviously, the multiple drugs of a combination regimen could be confusing and distracting to elderly patients, and could lead to poor treatment compliance. On the other hand, a well-designed combination pill that incorporates logical doses of two agents could enhance convenience and improve compliance.

Further potential value of combination treatment may result from the effects that two drugs have on each other’s pharmacokinetics. Although this has not been studied well, there might be situations where the clinical duration of action of the participating drugs becomes longer when used in combination than when they are administered as monotherapies. Finally, it is interesting to consider the attributes of such agents as ACE inhibitors, ARBs, and calcium channel blockers, which exhibit antigrowth or antiatherosclerotic actions in addition to their blood pressure-lowering properties. Is it

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<td>Increased antihypertensive efficacy</td>
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Source: From Ref. 106.
possible that combinations of these newer agents may provide even more powerful protective effects on the circulation?

**CONCLUSION**

A meta-analysis of nine trials with more than 15,000 elderly subjects reported that all-cause mortality, stroke mortality, and coronary mortality were reduced by lowering blood pressure (107). Elderly patients with hypertension, especially ISH, are the demographic group most likely to have uncontrolled hypertension. Despite clear evidence in elderly patients that morbidity can be reduced with antihypertensive drugs, clinicians are less aggressive with pharmacotherapy than they could be. The elderly also have concomitant diseases that often warrant major reductions in systolic blood pressure. Decreasing blood pressure in these age groups may be difficult. It has to be done carefully and although all of the guidelines suggest that the goal of systolic blood pressure should be less than 140 mg, this is not achievable in all patients. Blood pressure should also be lowered in patients with a previous stroke or transient ischemic attack (87).

Diuretics should probably be considered the first-line treatment for hypertension in the elderly unless other conditions exist (angina pectoris, diabetes mellitus, congestive heart failure), which may warrant treatment with other antihypertensive drugs (Table 6). With the stricter blood pressure goals, most patients will require combination antihypertensive regimens, especially for control of systolic blood pressure elevations (108).

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Disorders of Lipid Metabolism

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INTRODUCTION

The majority of coronary heart disease (CHD) mortality and morbidity occurs in individuals over 65 years of age (1) and cardiovascular disease accounts for nearly 70% of all deaths in this age group. Older patients have a particularly poor prognosis, and they are more likely to suffer disability following a cardiovascular event. In addition, older persons are more susceptible to stroke, which accounts for 1 in 15 deaths in the United States and is the leading cause of serious, long-term disability. The majority of strokes, 80%, occur in people over the age of 65 years. Finally, heart failure is of epidemic proportions in older persons and new data suggest that lipid lowering may provide benefit in these patients (1). Given increasing life expectancy and population aging, the number of individuals at risk of cardiovascular events, including CHD, heart failure, and stroke, is expected to increase. However, many older patients do not currently have their cardiovascular risk factors assessed or suitably controlled. While national and international guidelines consider age to be a risk factor for CHD (2), older persons are paradoxically less likely to receive aggressive primary and secondary prevention (3,4). The aim of this chapter is to review recent clinical trial data regarding lipid lowering in older individuals and to discuss current gaps in the treatment of older persons.

HYPERCHOLESTEROLEMIA AS A PREDICTOR OF CARDIOVASCULAR RISK

Hypercholesterolemia in older patients is a potentially important modifiable risk factor for cardiovascular events. It is highly prevalent and is associated with adverse clinical outcomes in younger subjects. Yet, the clinical significance of hyperlipidemia in the elderly has been the subject of much debate. While it is generally held that the relationship between CHD and cholesterol is continuous and graded, the results of several studies suggest that the strength of this relationship decreases markedly in patients over the age of 75. For example, some studies have indicated that the predictive value of cholesterol declines in patients older than 70 years (5,6), and have challenged whether cholesterol is relevant in older individuals (7). In contrast, several epidemiological
investigations of CHD have reported that risk factors in the middle-aged, including cholesterol, remain relevant than in older persons (8,9). Thus, the role of hyperlipidemia in older persons remains controversial.

In a cohort of men and women from the Established Populations for the Epidemiologic Studies of the Elderly, with mean ages of 78 and 79 years, respectively, Krumholz et al. found that the prevalence of total cholesterol levels greater than 240 mg/dL was 34% for women and 16% for men (5). There was no significant association between the total cholesterol level and the incidence of myocardial infarction (MI), unstable angina, CHD mortality, or all-cause mortality. In fact, the highest rates of MI were in the lowest cholesterol group. In women, survival was lowest in those with total cholesterol less than 200 mg/dL, while patients with total cholesterol greater than 240 mg/dL had the highest survival rate. In an age-specific analysis of the Framingham Heart Study, Kronmal demonstrated that as age increased, the relative risk associated with a high cholesterol level decreased (10). In this study, total cholesterol values peaked at about age 50 for men and at age 60 for women. Total cholesterol levels were higher in women of all ages. Low-density lipoprotein (LDL) cholesterol levels followed a similar age and gender pattern. The positive relationship between total serum cholesterol and all-cause mortality disappeared by age 60, and a significant negative relationship was evident at age 80. For an 80-year-old man with cholesterol greater than 240 mg/dL, five-year survival was 73%; if the cholesterol was less than 240 mg/dL, five-year survival declined to 49%. Corresponding five-year survival rates for women with cholesterol levels above or below 240 mg/dL were 74% and 70%, respectively. These relationships were not explained by coexisting illnesses. For CHD mortality, the relationship with total cholesterol remained positive, but the magnitude declined with age.

While these studies failed to detect a continuous relationship between cholesterol and CHD in the elderly, other prospective studies have reported significant, positive correlations between both total cholesterol and LDL cholesterol and CHD mortality and events in older patients. In white males aged 60 to 79 years enrolled in the Kaiser Permanente Coronary Heart Disease in the Elderly Study, Rubin et al. evaluated the CHD risk associated with high blood cholesterol (11). Independent of age, mortality from CHD rose with cholesterol levels. In male participants aged 65 to 74 years enrolled in the Honolulu Heart Program, CHD rates increased progressively with each quartile of cholesterol level (12). Total cholesterol was shown to be an independent predictor of CHD risk and this effect was not diminished with increasing age. In a cohort of elderly men and women in a long-term health care facility, mean age 82 years, Aronow et al. examined predictors of new coronary events. In this analysis, total cholesterol levels over 200 mg/dL in men and over 250 mg/dL in women were associated with an increase in coronary events (13). In a study of men and women aged 64 to 87 years in the Netherlands, total cholesterol was significantly associated with CHD mortality in women only. The Bronx Aging Study found that low high-density lipoprotein (HDL) cholesterol levels were a powerful predictor of CHD in elderly men, while high LDL cholesterol was a predictor of MI in elderly women (14).

In a review of 22 cohort studies, Manolio et al. found that total cholesterol and LDL cholesterol levels were significantly correlated with fatal CHD in both men and women across a broad range of populations including patients older than 65 years (15). While both the relative risk and the consistency of the relationship decreased with increasing age, these data suggest that high serum cholesterol confers an increased risk of CHD in patients up to 75 years of age. After age 75, the relative risk may drop off substantially, and few data exist to assess the effect of cholesterol on CHD risk in the very old (i.e., ≥85 years).
In a subgroup analysis of the Systolic Hypertension in the Elderly Program (SHEP), Frost et al. reported on the relationship between serum lipids and CHD in an elderly population with a mean age of 72 years. Multivariate analysis revealed that levels of total, non-HDL and LDL cholesterol were significantly related to CHD incidence during more than four years of follow-up. Specifically, a 40 mg/dL increase in total or LDL cholesterol was associated with a 30–35% increase in CHD events in this population (16).

There are several plausible explanations for discrepancies across studies in the relationship between cholesterol and outcomes in the elderly. Prevalent comorbidity and vulnerability to competing risks from other illnesses may confound the effects of cholesterol on CHD events (17). Cholesterol may have the strongest association with cardiovascular events in elderly patients at greatest risk, such as those with prior MI, but the association may be weak or nonexistent among patients in low risk subgroups. Few studies have included information on HDL or LDL lipoprotein cholesterol or on triglycerides, which would allow for a more refined assessment of risk. As noted earlier, it is especially relevant to examine the effect of risk factors on absolute risk in older patients. Since the number of coronary events increases with age, the risk of CHD events attributable to elevated cholesterol actually increases as individuals age, despite the fact that relative risk may decline. Viewed in this way, cholesterol is more, not less, important as a predictor of cardiovascular events in the elderly (11).

Epidemiological studies of the relation of lipoprotein levels to atherosclerosis in the elderly have concentrated primarily on coronary disease event rates, with little information concerning the impact of cholesterol on stroke rates. Until recently, cholesterol levels were not considered to be related to incident stroke in either younger or older individuals. With the advent of new imaging techniques that distinguish between hemorrhagic and atherothrombotic strokes, it has become clear that cholesterol levels are directly related to the incidence of atherothrombotic stroke, but inversely related to the incidence of hemorrhagic stroke (18). In Western societies, where most strokes are related to atherothrombosis, this observation may have particular significance for older patients.

CHOLESTEROL INTERVENTION AND CARDIOVASCULAR DISEASE PREVENTION

Relatively few studies have examined the impact of age on the efficacy of statins and other lipid-lowering drugs. However, a growing number of observational studies and randomized clinical trials with sufficiently large numbers of older persons indicate that statin therapy is equally efficacious in older and younger persons at high risk for cardiovascular events. Statins (3-hydroxy-3-methylglutaryl coenzyme A reductase inhibitors) reduce cardiovascular risk in a wide range of patients, and guidelines from both the American Heart Association/American College of Cardiology and the National Cholesterol Education Program Adult Treatment Panel III (NCEP ATP III) recommend statins as first-line therapy for the management of dyslipidemia, irrespective of patient age. As discussed below, not only are data emerging to support aggressive lipid lowering for the reduction of CHD events, but new data demonstrate the importance of lipid lowering in reducing cerebrovascular and peripheral vascular events as well.

Recent prospective observational studies support the use of statins in older persons, with 44% relative risk reductions in all-cause mortality being reported in patients aged 65 years and older in the Cardiovascular Health Study (19) and in patients aged 65 to 79 years in the Intermountain Heart Collaborative Study (20). In an analysis of a nationally representative cohort of over 40,000 older Medicare beneficiaries hospitalized with MI,
statins provided a mortality benefit at three years’ follow-up in patients up to age 83 (6). Similarly, a prospective study of 1410 patients aged 60 to 100 years (mean age 81 years) with prior MI and elevated LDL cholesterol in a long-term health care facility showed a 36% reduction ($p < 0.0001$) in the incidence of new coronary events in individuals treated with statins compared with those receiving no lipid-lowering medication, and these benefits were evident across all age ranges (21). Several other observational studies have also confirmed these findings. Multiple, large-scale randomized clinical trials have unequivocally demonstrated the effectiveness of statins not only in reducing LDL cholesterol, but also in improving clinical outcomes. Subgroup analyses of these trials as well as data from the Heart Protection Study (HPS) (22) indicate that statins reduce the risk of major coronary events irrespective of baseline cholesterol levels. More recently, the Treating to New Targets (TNT) (23) and the Pravastatin or Atorvastatin Evaluation and Infection Therapy—Thrombolysis in Myocardial Infarction 22 (PROVE IT-TIMI 22) studies have confirmed that a more intensive approach to lipid lowering provides incremental benefit beyond a more moderate lipid-lowering strategy in patients with stable CHD or high-risk acute coronary syndromes (ACS), respectively (24).

While it is clear that statins reduce coronary heart disease morbidity and mortality rates and increase overall survival in high-risk individuals younger than 75 years, the impact of statins in patients older than 75 years is less well delineated. In the Scandinavian Simvastatin Survival Study (4S), 4444 men and women up to age 70 with CHD were randomized to simvastatin or placebo and followed for up to 6.2 years. Simvastatin was associated with a 34% decrease in nonfatal MI and CHD death, a 42% decrease in CHD death alone, and a 30% decrease in all-cause mortality. Additionally, coronary procedures as well as cerebrovascular events were reduced in patients receiving simvastatin. These reductions in coronary and vascular endpoints were consistent across age, and there was no diminution of benefit as age increased (25). In the Cholesterol and Recurrent Events (CARE) study, 4129 patients up to age 75 with average cholesterol levels and who had an MI, 3–20 months before the start of the study, were randomized to pravastatin or placebo. The incidence of the primary combined endpoint of CHD death or nonfatal MI was reduced by 24% over a follow-up period of five years, and the benefits of pravastatin in preventing recurrent events were similar across age groups (26). The Long-Term Intervention with Pravastatin in Ischemic Disease (LIPID) trial (27) was a double-blind, randomized, placebo-controlled study of 9014 subjects, 39% of whom were older than 65 years and had acute MI or unstable angina within the previous 3 months to 3 years. The primary endpoint, coronary mortality, was reduced by 24% ($p < 0.0005$), and the secondary endpoint of total mortality was reduced by 22% ($p < 0.001$). Risk reductions also occurred in the incidence of MI (29%, $p < 0.00001$) and stroke (19%, $p = 0.048$) and in the rate of revascularization (20%, $p < 0.001$). Although the relative risk reduction with pravastatin was somewhat lower in patients aged 70 to 75 years, the absolute risk reduction was similar across age groups.

More recently, subgroup analyses from large randomized trials have also demonstrated that an aggressive lipid-lowering approach provides incremental benefit in older as well as younger patients. In the TNT study, treatment with atorvastatin 80 mg compared to atorvastatin 10 mg was associated with reductions in events in patients with stable CHD irrespective of age or sex. Similarly, in the PROVE-IT study, aggressive LDL lowering with atorvastatin 80 mg was associated with improvements in outcomes compared with moderate LDL reduction with pravastatin 40 mg in patients hospitalized with ACS. These results were also consistent irrespective of patient age or sex.

In the Anglo-Scandinavian Cardiac Outcomes Trial Lipid Lowering Arm (ASCOT-LLA) atorvastatin reduced the risk of nonfatal MI or fatal CHD by 36%, and the hazard
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The ratio for atorvastatin therapy was similar in patients older than 60 years (0.64; \( p = 0.0027 \)) and 60 years and younger (0.66; \( p = 0.0869 \)) (28). The Prospective Study of Pravastatin in the Elderly at Risk (PROSPER) specifically investigated the benefits of statin treatment in an older population \((n = 5804; \text{age} 70-82\text{ years})\) with or at high risk for vascular disease. Pravastatin treatment significantly decreased the risk of CHD death or nonfatal MI by 19% and reduced CHD mortality by 24% (29). There was, however, a significant 25% increase in incident cancer, a finding not confirmed in other studies. The recently reported Study Assessing Goals in the Elderly (SAGE) randomized 893 ambulatory patients aged 65 to 85 years (mean 72.5 years, 31% women) with CHD to receive atorvastatin 80 mg or pravastatin 40 mg daily and followed them for a 12-month period (30). All-cause mortality was 67% lower in the atorvastatin group \(( p = 0.014 \)) and there was also a nonsignificant 29% reduction in major cardiovascular events \(( p = 0.11 \)). Thus, the efficacy of statin treatment appears to be maintained in high-risk older patients.

These studies emphasize that statins are most beneficial in populations with greatest cardiovascular risk. Although relative risk reductions in older persons are similar to those observed in a middle-aged population, older patients are at greater absolute risk of cardiovascular events (25). Therefore, even small relative risk reductions can translate into larger absolute benefits. For example, in two large studies, although relative risk reductions were similar in patients 65 years and older compared with those younger than 65 years, absolute risk reductions were 1.5- to 2-fold greater in older patients (31).

The value of statin therapy in lower-risk older persons is the subject of debate. In the PROSPER study, the only trial specifically designed to assess the role of lipid lowering in older persons, pravastatin did not provide benefit in the primary prevention of cardiovascular events in lower-risk patients. However, a recent review of statin studies including PROSPER demonstrated that statins are beneficial in the primary prevention of disease even in patients at very low risk (32).

CHOLESTEROL INTERVENTION AND CEREBROVASCULAR DISEASE PREVENTION

The relationship between cholesterol and cerebrovascular events has been difficult to establish. However, data from the Honolulu Heart Study indicate that after adjustment for multiple comorbid conditions, low HDL cholesterol (<40 mg/dL) is associated with a significant hazard for subsequent stroke [hazard ratio (HR) 2.7]] compared with high HDL (>60 mg/dL). Epidemiologic data linking elevated LDL to cerebrovascular events is limited but recent studies and subgroup analyses of large randomized trials have explored the impact of statin therapy for the prevention of stroke.

Five major trials of statin therapy included patients without definite evidence of CHD: West of Scotland Coronary Prevention Study (WOSCOPS), Antihypertensive and Lipid Lowering Treatment to Prevent Heart Attack Trial-Lipid Lowering Trial (ALLHAT-LLT), HPS, ASCOT-LLA, and Collaborative Atorvastatin Diabetes Study (CARDS). Stroke was a component of the combined primary endpoint in CARDS and a secondary endpoint in the other trials. Active treatment reduced the risk of fatal and nonfatal stroke by 9% to 48%.

Similarly, long-term trials of statins that included approximately 90,000 patients with known CHD showed reductions in the relative risk of stroke of up to 50%. Consistent with reductions in the primary cardiovascular endpoints in these trials, statin therapy was associated with a 32% reduction in stroke in the CARE study, a 19% reduction in the LIPID study, and a 50% reduction in the Myocardial Ischemia Reduction with Aggressive
Cholesterol Lowering (MIRACL) study. In the HPS, simvastatin therapy was associated with a significant 27% reduction in stroke. Several meta-analyses have estimated the overall risk reduction in stroke to be approximately 15–30% (33,34). In addition, although not statistically significant, transient ischemic attacks (TIAs) were reduced by 25% in the PROSPER study ($p = 0.051$).

On the basis of these findings, the Stroke Prevention by Aggressive Reduction in Cholesterol Levels (SPARCL) trial was designed to address the question of whether statin therapy would reduce second stroke in stroke survivors (35). In this study, 4731 patients with stroke or TIA within six months, without known CHD, and with LDL cholesterol levels between 100 and 190 mg/dL were randomized to either atorvastatin 80 mg daily or placebo. The primary outcome was recurrent fatal or nonfatal stroke. Secondary endpoints included major coronary or cardiovascular events. Follow-up was planned for five years or until at least 540 events had occurred. The trial showed that high dose atorvastatin was associated with a 16% reduction in the risk of fatal or nonfatal stroke [HR 0.84 (0.71–0.99), $p = 0.03$]. Of note, recurrent strokes also tended to be less severe in patients treated with atorvastatin. In addition, major cardiovascular events were reduced by 35% in patients randomized to statin therapy [HR 0.65 (0.49–0.87), $p = 0.003$]. Given the significant burden of stroke in older persons, statins appear to be a reasonable approach for improving both cardiovascular and cerebrovascular outcomes.

CHOLESTEROL INTERVENTION AND VASCULAR DISEASE PREVENTION

Atherosclerotic vascular disease, including abdominal aortic aneurysm (AAA), renal artery stenosis, and peripheral arterial disease, is common in older persons and shares many risk factors with CHD, including elevated lipids. Increasing evidence supports the benefits of statin therapy in these disorders. For example, in the HPS, patients with peripheral arterial disease who were treated with simvastatin had a 19% reduction in the rate of new vascular events (22). LDL cholesterol has also been shown to be an independent predictor of the risk of AAA (36), and preclinical studies indicate that cerivastatin suppresses matrix metalloproteinase-9 production by inflammatory cells in the aneurysm wall (37). Hence, in addition to lipid-modifying effects, the anti-inflammatory actions of statins may have benefit for the prevention or treatment of AAA.

Dyslipidemia and other cardiovascular risk factors have been associated with an increase in the risk of aortic stenosis (38). Moreover, observational studies suggest that statin therapy may slow the rate of progression of aortic stenosis as measured by aortic valve area (39) or accumulation of aortic calcium (40). However, in a randomized trial involving 155 patients with calcific aortic stenosis, mean age 68 years, atorvastatin 80 mg daily failed to reduce the rate of progression compared with placebo over 25 months’ follow-up (41). More recently, an open-label study of 121 patients, mean age 74 years, with moderate aortic stenosis randomized to rosuvastatin 20 mg daily or placebo showed that rosuvastatin slowed the rate of echocardiographic progression of aortic stenosis during an average follow-up period of 17 months (42). In light of these conflicting results, the ongoing Simvastatin and Ezetimibe in Aortic Stenosis (SEAS) trial, which has randomized 1873 patients with asymptomatic aortic stenosis (mean age 68 years) to combination therapy with simvastatin 40 mg and ezetimibe 10 mg daily or to placebo, with a planned minimum follow-up of four years, should provide definitive information on the role of lipid-lowering therapy in older adults with moderate aortic stenosis (43).
CHOLESTEROL INTERVENTION AND COGNITIVE FUNCTION

Atherosclerosis is considered to be one of the mechanisms underlying the development of cognitive functional impairment in some patients (44), and elevated plasma cholesterol levels in middle age have been reported to increase the risk of Alzheimer’s disease later in life (45). In addition, several observational and cross-sectional studies have reported beneficial neurological effects with statins. For example, one cross-sectional study showed that statin treatment was associated with a 70% lower prevalence of dementia (46). A retrospective study of a community-based population also demonstrated an association between statin use and reduced rates of dementia (47). Similarly, a population-based Canadian survey found that lipid-lowering therapy was associated with a reduced risk of Alzheimer’s disease in patients younger than 80 years (48). Finally, in the Heart and Estrogen/progestin Replacement Study, cognitive impairment was associated with elevated LDL levels and patients receiving statin treatment recorded higher modified Mini-Mental State Examination (MMSE) scores and tended to have a lower likelihood of cognitive impairment than individuals not on statin therapy (49). Although these observations are promising, they have yet to be confirmed by prospective randomized trials. The effect of pravastatin treatment in older persons was investigated in PROSPER and no significant reduction in the risk of cognitive decline was reported.

CHOLESTEROL INTERVENTION AND HEART FAILURE

Heart failure (HF) is a major and growing public health problem worldwide (50,51). Cross-sectional and population-based studies indicate that at least one-third to one-half of all patients with HF have minimally reduced or preserved systolic function (PSF) (52). HF with PSF primarily affects older persons and is associated with poor prognosis (52). As the world population ages, the incidence and economic impact of HF with PSF will continue to increase. Unfortunately, no therapy to date has been shown to improve survival in these patients.

An emerging body of evidence suggests the potential value of statins in the management of patients with HF and reduced systolic function (53–56); however, data for patients with HF and PSF are very limited. A recent small single center study suggested that statin therapy may improve survival in patients with HF and PSF (57). In this study, 137 patients (68 on a statin and 69 on no statin) were followed for 21 ± 12 months. After adjustment for differences in baseline clinical variables between groups (hypertension, diabetes, coronary artery disease, and serum creatinine), statin therapy was associated with lower mortality (relative risk of death, 0.20; 95% CI, 0.06 to 0.62). However, the small sample size and single site nature of this study limit its generalizability.

There are several possible mechanisms by which statin therapy may produce beneficial effects in HF patients. Statin therapy has been shown to reduce myocardial necrosis and preserve myocardial viability (58), improve ventricular remodeling (59–62), prevent or even regress left ventricular hypertrophy and fibrosis (63), and down-regulate angiotensin type 1 receptors (64), all of which have important implications for HF patients. Statins may also improve left ventricular relaxation and diastolic function by decreasing left ventricular afterload via several mechanisms, including increasing arterial distensibility (65,66), improving endothelial function (67), decreasing blood pressure (59,60), modulating endothelial nitric oxide synthesis (61,62), and improving impaired autonomic nervous system activation (68). Most recently, statin use has been associated
with a reduced incidence of atrial fibrillation (69,70), a prevalent condition in older persons with or without HF.

SPECIAL CONSIDERATIONS FOR CHOLESTEROL INTERVENTIONS IN THE ELDERLY

The most recent edition of the National Cholesterol Education Program (NCEP) guidelines utilizes estimates of cardiovascular risk derived from Framingham tables relating levels of individual risk factors to coronary risk (71). In this scoring system, age is the single most potent predictor of risk. As a result, older individuals, even with only modest abnormalities of other risk factors, are more likely to fall into categories for which treatment with drugs to lower cholesterol is indicated. However, the decision to treat an older patient requires a careful balance between potential benefits and harms. Although statin therapy is effective in many older patients, some subgroups of older persons may not benefit. Kaplan-Meier curves from clinical trials indicate that the benefits of statin treatment can take up to one to two years to become apparent. Therefore, statin treatment may be unlikely to benefit patients with a short life expectancy (<2 years). However, persons aged 65 to 80 years in otherwise good health have sufficiently long life expectancies to benefit from statin treatment. Studies like PROSPER and HPS have improved the evidence base for statin treatment in patients up to and beyond 80 years of age and therefore help guide clinical decisions. Issues surrounding the underuse of statins in older persons need to be addressed, as these agents have been shown to be well tolerated and effective at reducing CHD morbidity and mortality.

Older individuals are particularly susceptible to adverse effects because they often receive concomitant medications, have comorbid conditions and competing risks, or may have impaired ability to metabolize and excrete compounds as a result of declining renal and hepatic function. Consequently, the safety of any lipid-lowering agent is particularly important for these patients, and physicians need to be aware of possible drug interactions.

Several overarching principles must be considered when treating older persons in general and with statins specifically. While older persons account for only 13% of the population, they account for more than one-third of individuals utilizing prescription drugs. It is estimated that older adults fill an average of 5.7 prescriptions per year. It is also estimated that approximately 15% of all hospitalizations in older persons are related to adverse drug reactions. The more medications a person is prescribed, the more likely it is that a drug-drug interaction or adverse drug reaction will occur. Thus, polypharmacy and the potential for drug-drug interactions are of the utmost concern in this patient population.

With aging, the pharmacokinetics of virtually all drugs are impacted and statins are no exception. This is due in part to the decline in total body water related to decreased muscle mass and the concomitant increase in total body fat, which ultimately affects the volume of distribution for almost all drugs. Water-soluble drugs are likely to have increased serum levels, while fat-soluble drugs have increased availability because of a prolonged half-life caused by the increased proportion of total body fat. To further complicate matters, there are variable changes in first-pass metabolism due to a variable decline in hepatic blood flow—thus elders may have less first-pass effect than younger persons, although this is difficult to predict on an individual basis. Moreover, oxidative metabolism through the cytochrome P450 (CYP) system declines with aging, resulting in decreased clearance of many drugs. This effect, coupled with increased likelihood of exposure to multiple medications that are metabolized through the P450 system, leads to increased potential for elevated serum levels of drugs and associated toxicity.
Despite these concerns, statin therapy is generally well tolerated in older persons. For example, simvastatin therapy was associated with relatively few side effects in the HPS, which included a large population of older patients who were taking concomitant medications (72). The Cholesterol Reduction In Seniors Program (CRISP) pilot study also showed that lovastatin 20 to 40 mg daily was associated with preserved health-related quality of life relative to placebo in a cohort of older adults with a mean age of 71 years (73). In a recent analysis from the TNT study, treatment with 80 mg of atorvastatin provided significant clinical benefit compared with 10 mg of atorvastatin in participants with stable coronary artery disease. There was a 2.3% absolute reduction in major cardiovascular events and a 19% relative reduction in risk favoring the high-dose group \(p = 0.032\). These findings support the use of intensive LDL cholesterol-lowering therapy in high-risk older persons with established cardiovascular disease (74).

Although the frequency of serious adverse events, such as severe myopathy, with statin treatment is low (<0.5%), older subjects may be more susceptible. Drug exposure in muscle tissue may be increased in older patients as a result of the age-related decline in muscle mass. In addition, hypothyroidism, which is more common in older persons, increases the risk of statin-induced myopathy. Hence, both physicians and patients should be alert to the presence of persistent myalgias, muscle tenderness, and particularly myoglobinuria. Physicians may be able to reduce the likelihood of adverse events by their choice of statin. It has been suggested that the lipophilicity of some statins may influence their entry into muscle tissue. Hydrophilic statins, such as lovastatin and pravastatin, are likely to penetrate muscle tissue to a lesser degree than lipophilic statins, such as atorvastatin, fluvastatin, and simvastatin, and may therefore be less likely to cause myotoxic events (75).

The potential for myotoxicity is also determined in part by systemic bioavailability, which is relatively low for statins (5–24%), and this limits the exposure of muscle tissue to these agents. The route of metabolism may also influence the likelihood of drug interactions and adverse effects. CYP 3A4 is the most abundant (60%) hepatic enzyme and is responsible for metabolizing the widest range of drugs (76). Thus, statins metabolized through pathways other than CYP 3A4 may be expected to have fewer drug interactions, which may be an advantage in older persons. However, the withdrawal of cerivastatin as a result of deaths due to rhabdomyolysis, particularly when coadministered with gemfibrozil, highlights the importance of drug interactions mediated by pathways other than CYP 3A4.

In addition to side effects and drug interactions, recent concerns have been raised over whether statin use may be associated with increased rates of certain cancers. In a meta-analysis of 26 randomized controlled trials of sufficient size and duration and which reported data on cancer diagnosis or cancer death, Dale et al. evaluated the effect of statins on cancer in general and on specific types of cancer (77). Individual statin brands as well as pharmacologic characteristics (hydrophilic vs. lipophilic, synthetic vs. natural) were also examined to determine whether there was heterogeneity in cancer effect. Among 86,936 participants included in the analysis, there were 6662 incident cancer cases and 2407 cancer deaths. No statistically significant differences were seen between patients randomized to statins compared with those randomized to control. In addition, there were no differences in cancer rates when the data were stratified according to cancer type, statin brand, dose, or pharmacologic characteristics. These results should reassure clinicians regarding the potential carcinogenic effects of statins, but they also emphasize that statins should not be viewed as effective anticancer agents. Despite the potential benefits of lipid lowering on cardiovascular events, many patients are not receiving optimal treatment, and undertreatment of lipid levels is especially prevalent in older individuals. For example, a 29% prevalence of lipid-lowering drug use
was observed in male CHD patients aged 60 to 75 years, and only 12% achieved total cholesterol levels recommended by the NCEP guidelines (6). Statin treatment appears to be prescribed preferentially to individuals under the age of 65 years, and an inverse relationship between age and the use of lipid-lowering medication has been observed in patients with CHD in the United States and Canada (78).

Several factors may contribute to lower statin prescription rates in older patients. As old age has traditionally been associated with high rates of mortality and morbidity, clinicians may believe that older persons are less likely to benefit from treatment. However, with the present high quality of health care and increased survival, many patients remain active and independent into old age. Another reason for undertreatment of lipids in older persons is a perceived lack of evidence that statins are effective or beneficial in this population. However, with the publication of HPS and PROSPER, there is now a strong scientific basis for treating patients aged 65 to 80 years, especially those at moderate or high risk for cardiovascular events. Similarly, many patients older than 80 years with cardiovascular disease or older than 65 years at risk for cardiovascular disease (i.e., primary prevention) are at sufficiently high risk to benefit from statin treatment, and better methods of identifying these individuals are required. Unfortunately, there is currently little scientific evidence to guide treatment decisions for very old patients (>85 years).

Another factor that may contribute to the underuse of statins is concern about the cost-effectiveness of treatment in this age group. However, studies indicate that the cost-effectiveness of statins is similar in younger and older patients. For example, analysis of CHD and stroke risk reductions with statin treatment for secondary prevention indicate incremental cost-effectiveness ratios ranging from $4675 to $20,987 per year of life gained in men and women 40 years of age, and from $7447 to $21,719 in men and women 70 years of age (79). All of these estimates are well within the generally accepted cost-effectiveness benchmarks in the United States of $50,000 to $100,000 per year of life gained.

Adherence to therapy can be particularly poor in older patients owing to polypharmacy, medication costs, depression, or cognitive decline. Physicians may improve compliance by educating patients and their families or caregivers about the importance of adhering to therapy. The use of more efficacious, well-tolerated statins enabling a greater proportion of patients to achieve cholesterol targets on the initial dose, thereby reducing the need for titration, may aid compliance in both older and younger patients.

**HDL CHOLESTEROL**

Although LDL cholesterol is considered the predominant atherogenic lipoprotein in the development of CHD, there is considerable variability in the clinical expression of CHD at any given LDL concentration. HDL cholesterol levels exhibit a continuous and inverse relationship with CHD events, although data in older persons are scant.

In the Framingham Heart Study, a low level of HDL was an independent predictor of CHD (80). In fact, at all levels of LDL cholesterol, the level of HDL influenced the risk of developing CHD. In men with HDL levels less than 25 mg/dL, the CHD incidence over four years was 180/1000 compared with 25/1000 in men with HDL levels greater than 64 mg/dL. A similar relation was noted in women, and these relationships persisted above the age of 60 years. Other studies have reported similar findings. In general, a 1 mg/dL increase in HDL is associated with a reduction in CHD risk of approximately 2% in men and 3% in women. The HDL level has no effect on noncardiovascular disease mortality.

The Lipid Research Clinics Coronary Primary Prevention Trial (81–84) using cholestyramine and the Helsinki Heart Study (85) using gemfibrozil both demonstrated that increasing HDL lowered CHD events, and this association was independent of any
effect on LDL. More recently, the VA HDL Intervention Trial (VA-HIT) and Bezafibrate Infarction Prevention (BIP) trial demonstrated that increasing HDL reduces CHD mortality (86,87). The ATP III of the NCEP identifies low HDL cholesterol as a major risk factor for CHD and recommends that all healthy adults be screened for both total cholesterol and HDL cholesterol levels.

**Triglycerides**

The independent relationship between plasma triglycerides (TGs) and CHD has now been established (88), although data in older persons are again limited. It is likely that the defective lipoprotein metabolism involved in hypertriglyceridemia may create a vascular environment predisposed to atherogenesis. Elevated fasting plasma TG is a hallmark of insulin resistance syndrome, a metabolic disorder characterized by hyperinsulinemia, glucose intolerance, decreased HDL, and possibly central obesity and increased production of atherogenic, small, dense LDL particles.

Data from the observational Prospective Cardiovascular Muenster (PROCAM) (89) study showed that CHD risk is high when TG levels exceed 200 mg/dL and the total cholesterol/HDL ratio is greater than 5 because of low HDL (<35 mg/dL). In this eight-year prospective study of 4639 German males, aged 40 to 65 years, the incidence of major coronary events steadily increased in association with rising TG levels up to 800 mg/dL. Patients with TG > 200 mg/dL had at least twice the coronary event rate as patients with normal TG levels. However, despite these data, and the fact that fibric acid derivatives, nicotinic acid, and fish oil capsules effectively lower TGs, there is currently no evidence that treatment of elevated TG levels lowers cardiovascular risk. For this reason, TGs are considered a secondary target for lipid-lowering therapy in current NCEP guidelines.

**NONSTATIN APPROACHES TO LIPID LOWERING**

**Diet**

A proper diet, rich in fruits, vegetables, and whole grain foods and low in saturated and transsaturated fats, is an integral component of lipid-lowering therapy. NCEP and American Heart Association (AHA) guidelines promote a diet in which fat composes 30% or less of total calories. Based on recommendations from the World Health Organization, the AHA suggests that fat calories constitute no less than 15% of total calories. A change from the average American diet to the AHA’s Step-One Diet, in which less than 10% of total calories are derived from saturated fatty acids and dietary cholesterol intake is less than 300 mg/dL, reduces serum cholesterol levels by approximately 7%. Further restriction to less than 7% of calories from saturated fatty acids and less than 200 mg/dL of cholesterol (Step-Two Diet) reduces cholesterol levels by an additional 3% to 7%.

**Exercise**

Regular exercise is important for maintaining cardiovascular fitness, particularly in older adults, and low levels of physical activity are associated with an increased risk for both cardiovascular events and all-cause mortality. However, large epidemiologic studies have failed to demonstrate a consistent correlation between reported physical activity and lipid values. On the other hand, exercise interventions have been shown to improve functional capacity, raise HDL, and lower TG levels, thereby favorably altering the cardiovascular risk profile. In addition, exercise-based cardiac rehabilitation programs reduce the risk of
recurrent cardiac events, including death, following acute MI or coronary bypass surgery. Therefore, regular exercise is recommended in conjunction with a healthy diet and weight loss as part of an overall strategy for improving health and reducing cardiovascular risk.

Pharmacotherapy

Currently, LDL remains the principal target for intervention, and efforts to reduce cardiovascular risk should first focus on reducing LDL cholesterol in accordance with existing guidelines. HDL, TGs, and non-HDL cholesterol (i.e., total cholesterol – HDL cholesterol) levels are secondary targets for intervention once the appropriate LDL level has been achieved. Unfortunately, because of the paucity of clinical trials addressing either HDL-raising or TG-lowering therapies, evidence-based recommendations are lacking, and data in older persons are essentially nonexistent. Beyond statins, pharmacological interventions include nicotinic acid, fibric acid derivatives, and ezetimibe. Each has a unique mechanism of action and potential side effect profile in older persons.

Nicotinic Acid

Nicotinic acid (niacin) is a B vitamin that inhibits adenylate cyclase when administered in high doses, thereby affecting the lipoprotein system mediated through nicotinamide adenine dinucleotide (NAD), or NADP. Rapid release of prostaglandins from platelets is thought to be responsible, in part, for the vasodilation and flush response commonly associated with high dose niacin therapy. Nicotinic acid exerts favorable effects on HDL, TGs, TG-rich lipoproteins, total cholesterol, LDL, LDL subclass pattern B, and possibly lipoprotein(a) [Lp(a)]. In daily doses of 1500 to 3000 mg, nicotinic acid typically reduces total cholesterol and LDL levels by 10% to 25% and TG levels by up to 50%, while increasing HDL by 15% to 30%.

Nicotinic acid is the lipid-altering drug with the most potential for side effects and, consequently, adherence problems. However, given the potential benefits of the drug, it is worth expending extra effort to achieve compliance in well-selected individuals. Slowly titrating the dose from 100 to 500 mg three times a day over a one-month period can ease the patient into a therapeutic dose range. The prostaglandin-mediated flush reaction, which occurs in up to 50% of patients, can be ameliorated in part by ingesting 2.5 grains (162.5 mg) of aspirin 15 minutes prior to niacin dosing. Avoiding alcohol, monosodium glutamate, hot beverages, and spicy foods can also help minimize flushing. Once daily sustained-release niacin preparations also appear to be associated with less flushing, especially when taken at bedtime.

Other side effects from high dose niacin include a small increase in the serum glucose level (average 6%), a moderate increase in the serum uric acid level, and a small reduction in the serum phosphorus level. Significant elevations in hepatic transaminases are uncommon with niacin monotherapy.

Combination Therapy with Statins and Nicotinic Acid

Several large studies have assessed the effects of combining a statin with nicotinic acid. In the Arterial Biology for the Investigation of the Treatment Effects of Reducing Cholesterol (ARBITER) 2 study (90), niacin (1000 mg/day) was added to statin therapy (majority of subjects used simvastatin) in persons with known CHD. The mean age of the study population was 67 ± 10 years, and 91% were men. Progression of carotid intimal-medial
thickness was significantly less in subjects using the statin-niacin combination compared to a statin alone. LDL cholesterol levels were less than 100 mg/dL in both groups, while HDL increased significantly (17%, \( p = 0.003 \)) and TG decreased significantly (18%, \( p = 0.03 \)) in the statin-niacin group. Fasting glucose levels increased in both groups, while flushing was more common in the statin-niacin group.

In another study (91), the effect of statin-niacin therapy on calcified plaque progression was assessed in subjects without known CHD. The investigators found no difference in calcium burden as assessed by electron beam computed tomography between statin-only and statin-niacin therapy. HDL cholesterol increased in the statin-niacin group, while levels of LDL, non–HDL cholesterol, TGs, and total cholesterol: HDL decreased significantly. In a more recent study assessing the effects of rosuvastatin and extended-release niacin (92) in subjects with mixed dyslipidemia, the rosuvastatin/extended-release niacin combination was well tolerated and significantly reduced total cholesterol and TG levels while increasing HDL levels.

**Fibric Acid Derivatives**

Fibric acid derivatives (fibrates) enhance lipoprotein lipase activity and hepatic bile secretion and reduce hepatic TG production. TG reductions between 8% and 72%, LDL reductions between 1% and 35%, and HDL increases between 1% and 25% have been reported. These agents are useful in the treatment of hypertriglyceridemia and in selected patients who have elevated LDL in combination with elevated TGs. The HDL level often increases when the initial HDL is low. In the Helsinki Heart Study, gemfibrozil 600 mg twice daily resulted in an overall 42% reduction in TGs, 10% reduction in LDL, and a 10% increase in HDL (85). These effects led to a 34% reduction in the incidence of CHD, although there was no difference in total mortality (93).

Fibrates are generally well tolerated. Occasionally, mild nausea is experienced during the first week of therapy. To reduce this potential side effect, it can be useful to start treatment with one-half the normal dose for several days before increasing to a full dose. Fibric acid derivatives are excreted primarily through the kidney; therefore the dose should be adjusted in patients with chronic kidney disease. In addition, warfarin should be dosed at one-third its standard dose when administered with fenofibrate, with careful follow-up of the international normalized ratio. Glucose tolerance is not impacted by this agent, and no lithogenic potential has been observed. Creatine phosphokinase elevations are noted in 0.6% to 1.1% of cases, usually in association with renal failure. Liver enzymes increase in less than 2% of cases, whereas gastrointestinal disturbances (constipation, dyspepsia, and diarrhea) account for over 50% of side effects, leading to discontinuation in 3.5% of patients.

**Combination Therapy with Statins and Fibrates**

Product information for statins and fibrates generally states that combination therapy with these agents is not recommended, owing to an increased risk of myopathy. Combination therapy must be used with care and should probably be avoided in all but the healthiest older people. In particular, patients with acute or serious chronic illness (especially renal disease), those requiring surgery, and those on multiple medications or cyclosporin, macrolides, or antifungals, should not take both a statin and a fibrate. However, despite these precautions, excellent therapeutic responses can be achieved with appropriate safety monitoring.

In a literature review regarding the safety of combination therapy with statins and fibrates in the treatment of mixed hyperlipidemia in patients aged 44 to 64 years (mean
For all trials, age for all trials, 53.3 ± 5.6 years, the incidence of myopathy was 0.12% (defined as creatine kinase levels >10 times the upper limit of normal) (94). Musculoskeletal symptoms (myalgia, muscle weakness, musculoskeletal pain, or myositis) occurred in 1.9%, subclinical elevations of creatine kinase (elevations <10 times the upper limit of normal) occurred in 2.1%, and subclinical elevations of serum transaminases (elevations <3 times the upper limit of normal) occurred in 3.2%. Gemfibrozil was the most prescribed fibrate (56%) in this study, whereas fenofibrate usage accounted for only 6% of the total (the remainder of the fibrates used, including bezafibrate and ciprofibrate, are not available in the United States). Overall, older age, female gender, renal or liver disease, diabetes, hypothyroidism, debilitated status, surgery, trauma, excessive alcohol intake, and heavy exercise were associated with increased risk for myopathy.

**Ezetimibe**

Ezetimibe selectively inhibits the intestinal absorption of cholesterol and related phytosterols. Administered alone or in combination with a statin, ezetimibe is indicated as adjunctive therapy to diet for the reduction of elevated total cholesterol, LDL, and apolipoprotein B in patients with primary hypercholesterolemia. Mechanistically, the combination of a statin, which inhibits hepatic cholesterol synthesis, and ezetimibe, which blocks intestinal cholesterol absorption, is attractive (95,96), and several studies have shown that combination therapy is more effective than either drug class alone in lowering total cholesterol and LDL levels, and in achieving target LDL levels recommended by current guidelines (95–106). The effect of this strategy on cardiovascular outcomes, however, has not been established.

Ezetimibe is generally well tolerated. When coadministered with a statin, elevations in serum transaminases (>3 times the upper limit of normal) occur slightly more frequently (1.3%) than with a statin alone (0.4%). Therefore, liver function tests should be monitored when ezetimibe is added to statin therapy. Rhabdomyolysis has been reported very rarely with ezetimibe monotherapy or when ezetimibe has been added to a statin. The safety and effectiveness of ezetimibe in combination with fibrates have not been established; therefore, coadministration with fibrates is not recommended. In addition, limited data are available on the use of ezetimibe in older adults, either as a single agent or in combination with a statin.

**CONCLUSION**

With increases in life expectancy and the rapid growth of the population over the age of 80 years, it has become imperative to maintain quality of life and reduce morbidity. Data from several studies indicate that statin treatment reduces total and LDL cholesterol levels and the risk of cardiovascular disease as effectively in older high-risk individuals as in younger individuals. However, despite these benefits, a substantial proportion of older individuals at risk for cardiovascular events are not receiving evidence-based lipid-lowering therapy. Physicians should use clinical judgment in determining who should receive lipid-lowering treatment, basing their decisions on patient preferences, individual outcome goals, life expectancy, and quality of life, coupled with the anticipated benefits and potential risks of therapy, including cost-effectiveness. Further studies exploring the role of lipid lowering in the very old as well as in primary prevention of cardiovascular disease in older persons are necessary. For now, a large body of consistent data indicates that patients should not be denied lipid-lowering therapy solely on the basis of age.
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Disorders of Lipid Metabolism


7

Diabetes Mellitus and Cardiovascular Disease in the Elderly

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Diabetes mellitus is the most common metabolic disorder in the United States, affecting over 20 million persons, and more than 650,000 new cases are diagnosed annually (1,2). More than 100 million people are affected worldwide; approximately 90% of these have the non-insulin-dependent type of the disease. The prevalence of diabetes mellitus increases with advancing age and is estimated to be 20% in Caucasians older than 75 years. Because of its serious long-term complications, diabetes mellitus has become a major public health problem (3,4). The sequelae of diabetes mellitus are commonly divided into microvascular (mainly retinopathy, nephropathy, and neuropathy) and macrovascular (atherosclerotic disease of the coronary, cerebral, and peripheral arterial circulation).

Multiple clinical studies over the years have documented the increased risk of diabetic patients to develop cardiovascular disorders. The Framingham Study of more than 5000 subjects showed diabetes mellitus to be a powerful risk factor for atherosclerotic coronary and peripheral vascular diseases with relative risks (RR) averaging twofold for men and threefold for women (5). The Framingham Study also showed that the risk of stroke is 2.5 times higher than average in diabetics (6). These findings have been confirmed by other epidemiological studies such as the Honolulu Heart Program, the Copenhagen Stroke Study, the Rancho Bernardo Study, and the Monitoring of Trends and Determinants in Cardiovascular Diseases (MONICA) study (7-9). More recently, a population-based study of elderly patients concluded that diabetes mellitus is also an independent risk factor for heart failure and that the risk of heart failure increases with disease severity (10).

In a recent meta-analysis of 37 prospective studies that included 447,064 patients, the overall rate of fatal coronary heart disease (CHD) during follow-up periods ranging from 4 to 36 years was 5.4% for diabetics versus 1.6% for nondiabetic patients (11). Because of the compelling evidence of the impact diabetes has on the development of CHD, it has been upgraded in the most recent version of the Adult Treatment Panel (ATP) III of the National Cholesterol Education Program (NCEP) guidelines from a simple cardiovascular risk factor to a CHD-risk equivalent; this means that the future cardiovascular risk of a diabetic is comparable to that expected in a patient with established atherosclerotic disease (12).
Epidemiological studies of diabetes mellitus have shown that gender, age, and ethnic background are important factors when considering the development of diabetic complications. In a population study from Sweden of diabetes as a risk factor for acute myocardial infarction (MI), the prevalence of diabetes was 5% in men and 4.4% in women (13). The RRs for MI were 2.9 [confidence interval (CI) 2.6–3.4] in diabetic men and 5.0 (CI 3.9–6.3) for diabetic women. Overall acute MI mortality was four times higher in diabetic men and seven times higher in diabetic women. These and other data have led to the concept that diabetes mellitus causes a loss of the “female advantage” for women (14). However, this concept has recently been challenged. In a meta-analysis of 16 studies, Kanaya et al. found that there was no excess risk of CHD mortality in diabetic women after adjusting for classic CHD risk factors; moreover, men had more CHD deaths attributable to diabetes than women (15).

The clinical and economic burden of diabetes mellitus and its complications increases with advancing age. For example, in a group of patients with a mean age of 80 ± 8 years seen in an academic geriatric practice in 2003 (16), the overall prevalence of diabetes was 17%, and the prevalence of target organ damage and/or clinical cardiovascular disease was 85% among the 335 patients with diabetes mellitus. In this elderly group of diabetic patients, 44% had coronary artery disease, 28% had sustained cerebrovascular accidents or transient ischemic attacks, 26% had peripheral vascular disease, 75% had hypertension, 90% had hypertension or hyperlipidemia, 19% had congestive heart failure, 32% had nephropathy, and 20% had retinopathy. The prevalence of diabetes mellitus was highest among Hispanics (29%), lowest in whites (11%), and intermediate in African-Americans (21%).

The overall costs of diabetes mellitus constitute a major burden on the United States and worldwide economies. In addition to being a significant cause of cardiovascular disease, diabetes is the leading cause of renal failure in the United States and is responsible for over one-half of the nontraumatic lower limb amputations performed annually (17). Direct and indirect costs of diabetes mellitus account for nearly 15% of total U.S. health care expenditure and were estimated at $132 billion in 2002 (18). Direct medical expenditures totaled to $91.8 billion, including $23.2 billion for diabetes care, $24.6 billion for chronic complications attributable to diabetes, and $44.1 billion for excess prevalence of chronic medical conditions. Of the estimated total $91.8 billion health care expenditures attributable to diabetes, 52% was for services provided to persons 65 years of age or older. These costs are primarily due to the macrovascular and microvascular complications of type 2 diabetes mellitus. In a retrospective cohort study from a large health maintenance organization, the average annual cost of health care for a patient over the age of 65 was $3400 (in 1995). Excess expenditures (expressed as a multiple of the average annual cost) for patients with diabetes mellitus ranged from 1.6 times in those with no diabetic complications to 4.1 times for those with MI, 4.0 times for those with foot ulcers, and 4.3 times for those with end-stage renal disease (19). These data support the notion that early and aggressive preventive and therapeutic interventions in patients with diabetes mellitus and cardiovascular disease are desirable for economic as well as clinical reasons.

PATHOPHYSIOLOGY AND BIOCHEMICAL DEFECT OF DIABETES MELLITUS AND INSULIN RESISTANCE

The current classification of diabetes as either type 1 or type 2 is based on the pathophysiological differences between the two syndromes. In type 1 diabetes, hyperglycemia occurs because of the complete inability to produce insulin. In type 2
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diabetes, hyperglycemia is the result of impaired insulin release and an increased resistance to insulin. The majority of the U.S. diabetic population has type 2 diabetes (over 90%). The pathogenesis of both forms of diabetes is complex, being influenced both by genetic and environmental factors.

Type 1 Diabetes Mellitus

Type 1 diabetes mellitus results from the autoimmune destruction of pancreatic insulin-secreting β cells within the islets of Langerhans. Islet-cell autoantibodies are detected in 80% of patients with newly diagnosed type 1 diabetes, and the measurement of serum islet-cell autoantibodies is a screening test to determine patients at risk for this disorder (20).

The importance of genetics in the development of type 1 diabetes is supported by the observation that the incidence is increased in relatives of type 1 diabetics. Whereas the lifetime risk for type 1 diabetes is 6% in children, the risk is only 0.4% in families with no diabetes history. An identical twin has a 30% lifetime risk of developing diabetes, while a sibling or fraternal twin has a 5% risk (21). Although four genes have been identified that increase the susceptibility to type 1 diabetes, none of these genes directly induces the disease. The role of environmental factors in the pathogenesis of type 1 diabetes is suggested by twin studies, which have demonstrated that when one monozygotic twin is affected, the other twin is affected less than 50% of the time.

Type 2 Diabetes Mellitus

Similar to type 1 diabetes mellitus, the pathogenesis of type 2 diabetes is multifactorial, with its development influenced both by environment (particularly diet, obesity, increased visceral fat, advanced age, low exercise level) and genetics (specifically the combined effects of multiple gene alterations). The majority of type 2 diabetics are obese and over the age of 40. Unlike absolute absence of insulin in type 1, type 2 diabetes mellitus is characterized by a combination of both relative deficiency of insulin and insulin resistance. Type 2 diabetes develops when the resistance to insulin activity is no longer compensated by increased insulin production from poorly functioning pancreatic islet β cells. Indeed, insulin resistance may be the best predictor of future type 2 diabetes (22). Sedentary lifestyle and obesity dramatically increase the risk of type 2 diabetes by increasing insulin resistance.

Specific biochemical changes affect the prevalence of type 2 diabetes in the elderly. The presence of inflammation as measured by C-reactive protein (CRP) and other pro-inflammatory cytokines has been associated with the development of diabetes in the elderly (23–25). Conversely, high levels of adiponectin—an adipocytokine that increases insulin sensitivity—are associated with a reduced incidence of diabetes in older age groups (24).

Insulin Resistance and Insulin Resistance Syndrome

Insulin resistance is the physiological state in which a normal amount of insulin produces a subnormal physiological response. Lean nondiabetic subjects are two times more sensitive to insulin than obese nondiabetic subjects and obese type 2 diabetics are more insulin-resistant than obese nondiabetic subjects (26). Plasma insulin levels increase as a result of a deficient peripheral tissue response to insulin-mediated glucose metabolism. Insulin resistance occurs early in pre-type 2 diabetics and a majority, but not all, of insulin-resistant individuals will progress to overt type 2 diabetes. Insulin resistance is
most closely associated with acquired or lifestyle factors as obesity, aging, pregnancy, and physical inactivity (27), with currently identified gene mutations accounting for only a small minority of insulin resistance cases. In addition to being one of the major pathophysiological abnormalities in type 2 diabetes, insulin resistance promotes an atherogenic lipid profile, endothelial dysfunction, increased sympathetic nervous system activity, impaired fibrinolysis, and a hypercoagulable state (28). The Helsinki Policemen Study (29) demonstrated that insulin resistance alone was a predictor of CHD.

Insulin resistance syndrome, also referred to as the metabolic syndrome, is a clinical syndrome defined by the presence of three or more of the following five abnormalities (12): (i) abdominal obesity (female waist circumference greater than 35 inches and male waist circumference greater than 40 inches); (ii) triglycerides greater than 150 mg/dL; (iii) high-density lipoproteins (HDL) less than or equal to 40 mg/dL in men or less than or equal to 50 mg/dL in women; (iv) hypertension (blood pressure ≥130/85 mmHg); and (v) hyperglycemia (fasting blood glucose ≥110 mg/dL). These parameters are often observed in the obese, prediabetic individual. The overall prevalence of the metabolic syndrome in the United States is 22%, with an age-dependent increase (6.7%, 43.5%, and 42.0% for age groups 20 to 29, 60 to 69, and >70 years, respectively) (30). The World Health Organization and the International Diabetes Federation have proposed slightly different criteria for the metabolic syndrome (31,32), and the European Group for the Study of Insulin Resistance has suggested that a more appropriate name would be the “insulin resistance syndrome” (33).

Patients with the metabolic syndrome are at significantly increased risk of coronary artery disease as demonstrated by the Kuopio Ischemic Heart Disease Risk Factor Study (34). In this Finnish, population-based, prospective cohort study, 1209 men without preexisting coronary disease or diabetes were tested for metabolic syndrome and followed for a mean of 11.4 years. Men with metabolic syndrome were 2.9 (95% CI 1.2–7.2) to 4.2 (95% CI 1.6–10.8) times more likely to die of ischemic heart disease after adjustment for conventional cardiac risk factors.

Although there is ongoing debate as to what precisely constitutes the metabolic syndrome and whether it is in fact a true syndrome, the current obesity epidemic in the United States has thrust it into the forefront of public health efforts to reduce the incidence of type 2 diabetes and CHD (35). Numerous clinical studies have produced compelling data regarding the importance of weight loss, exercise, and a healthy diet. In both the Diabetes Prevention Program (36) and the Finnish Diabetes Prevention Study (37), behavior modification interventions in patients with impaired glucose tolerance produced an identical 58% reduction in the progression to type 2 diabetes. A secondary analysis of the Diabetes Prevention Program showed that over 3.2 years the prevalence of the metabolic syndrome decreased from 51% to 43% in the lifestyle intervention group and increased from 55% to 61% in the usual care group, demonstrating that lifestyle modification is effective in delaying or preventing the development of both the metabolic syndrome and type 2 diabetes (38).

CARDIOVASCULAR COMPLICATIONS OF DIABETES MELLITUS

Pathophysiological Changes

The complications of diabetes mellitus have traditionally been divided into two major categories: (1) microvascular complications including retinopathy, neuropathy, and nephropathy and (2) macrovascular complications including coronary artery disease,
cerebrovascular disease, and peripheral arterial disease (PAD). The microvascular complications are unique to diabetes, whereas the macrovascular findings are similar in patients with and without diabetes.

Microvascular Pathophysiology

Chronic hyperglycemia is a major initiator of microvascular complications. Two studies, the Diabetes Control and Complications Trial (DCCT) and United Kingdom Prospective Diabetes Study (UKPDS), demonstrated that aggressive control of hyperglycemia reduces the onset or progression of nephropathy, retinopathy, and neuropathy associated with type 1 and type 2 diabetes (39,40). Cardiac microvascular dysfunction is manifested by impaired autoregulation of coronary blood flow and vascular tone in the absence of significant epicardial coronary artery disease, with a resultant reduction of maximal coronary blood flow and coronary flow reserve (41,42).

Although no occlusive lesions in the diabetic coronary microcirculation have been demonstrated, other structural changes (medial hypertrophy, perivascular fibrosis, and intimal hypertrophy) have been documented (43). These histopathological changes in conjunction with impaired endothelial function at the microvascular level may explain the higher frequency of silent ischemia, exercise thallium defects, myocardial fibrosis, and left ventricular dysfunction in diabetics in the absence of occlusive epicardial coronary disease (44).

Macrovascular Pathophysiology

Diabetes mellitus accelerates atherosclerosis via chronic hyperglycemia, insulin resistance, and dyslipidemia. Both hyperglycemia and insulin resistance impair endothelium-dependent vasodilation by decreasing the nitric oxide formation (45). Increased levels of endothelin-1 in diabetics stimulate vasoconstriction, induce vascular smooth muscle hypertrophy, and activate the renin-angiotensin system (46). Diabetes promotes the accumulation of foam cells in the subendothelial space by increasing the production of leukocyte adhesion molecules and proinflammatory mediators (47). Plaque instability and rupture is increased in diabetics as a result of decreased synthesis and increased breakdown of the collagen that plays a critical role in reinforcing the fibrous cap of vulnerable plaques (48,49).

In addition to the atherosclerotic effects of diabetes upon the arterial wall, the hematologic system is adversely affected. Diabetes promotes platelet activation by increasing platelet-surface expression of glycoprotein Ib, which mediates binding to the glycoprotein IIb/IIIa (GpIIb/IIIa) receptor and to the von Willebrand factor (50). Inhibitors of platelet activity, including platelet-derived nitric oxide and endothelial prostacyclin, are decreased in diabetes. Diabetes also increases coagulation activity by stimulating production of procoagulants such as tissue factor and by reducing levels of anticoagulants such as protein C and antithrombin III (51,52). Furthermore, decreased levels of plasminogen activator type 1 in diabetics result in impaired fibrinolysis (53).

Clinical Consequences of Diabetes Mellitus

Coronary Heart Disease

The Framingham Study demonstrated that diabetes is a powerful predictor of CHD with an average twofold increase in risk for men and threefold for women (54). The elderly diabetic patient is at particularly high risk for coronary heart disease; in one study 44% of
octogenarians with diabetes were found to have CHD (16). Diabetic women are also at increased risk for CHD, experiencing a CHD mortality rate similar to that of diabetic men, and a five- to sevenfold higher rate of CHD mortality compared with age-matched, nondiabetic women (55). These and other data suggest that diabetes may abrogate the so-called female advantage for CHD mortality, thus accounting for the higher CHD rates in premenopausal diabetic women (14,56). The excess mortality from CHD in diabetic women compared with diabetic men increases with advancing age. In the MONICA study, the attack rate for acute MI increased almost 10-fold for diabetic women aged 55 to 64 years compared with those aged 45 to 54 years, whereas the increase was only twofold in male subjects (13).

More recently, a population-based autopsy series from the Mayo Clinic characterized coronary atherosclerosis in 293 diabetic and 1736 nondiabetic subjects with a mean age of 73 and 75 years, respectively, and a male-to-female gender ratio of approximately 1:1. The study demonstrated that among diabetic decedents without clinical CHD, almost 75% had high-grade coronary atherosclerosis and more than half had multivessel disease. Nondiabetic women had less atherosclerosis than men, but the female advantage was lost with diabetes regardless of age. In addition, diabetic decedents without clinical CHD had a prevalence of high-grade atherosclerosis similar to that observed in nondiabetic decedents with clinical CHD (57).

Although diabetes leads to increased incidence of CHD and MI, controversy continues as to whether the distribution of coronary artery disease is different in diabetics than in nondiabetic patients. Some investigators have found that diabetics referred for intervention (surgical or percutaneous) have diffusely diseased, frequently inoperable vessels (58). Others have reported a higher incidence of left main coronary artery disease (13% vs. 6% in diabetics vs. nondiabetics), while still other investigators have found more triple-vessel disease in diabetics (43% vs. 25%) than in nondiabetics (59). However, other studies have found no difference in the distribution of coronary artery disease in diabetics compared with nondiabetic populations (60,61).

Diabetes is associated with an increased prevalence of silent ischemia and unrecognized MI. In a study from Marseilles, France, the prevalence of silent ischemia was found to be approximately 30% in type 2 diabetic men with established CHD, while the prevalence in nondiabetic patients was 1% to 4% (62). Similarly, in a study by Naka, diabetics had a 2.2 times higher prevalence of silent myocardial ischemia compared with nondiabetic controls with established CHD (63). Both the Framingham (64) and World Health Organization (65) epidemiological studies have reported an increased incidence of asymptomatic MI in the elderly. Aronow and Epstein demonstrated silent myocardial ischemia by Holter monitoring in 34% of an elderly group of patients residing in a home for the aged (66). It is, therefore, likely that the elderly diabetic patient is particularly prone to harbor asymptomatic CHD.

More recently DeLuca et al. conducted a retrospective chart review of 287 patients with diabetes (71% men; mean age 83 ± 8 years) and 292 age- and gender-matched patients without diabetes (67). Of the diabetic patients without prior history of MI, 18% were diagnosed as having had a prior unrecognized infarct compared with 7% of those without diabetes (p < 0.001). Similarly, silent myocardial ischemia was diagnosed in 33% of those with diabetes compared with 15% of those without (p < 0.001). Thus, even at an advanced age, diabetic patients have a higher prevalence of unrecognized MI and silent myocardial ischemia than patients without diabetes. The mechanisms responsible for silent ischemia in diabetes are not well understood but may include altered pain threshold, autonomic neuropathy leading to sympathetic denervation, higher production of β endorphins, and other factors (68–70).
There is currently no consensus as to whether a broad-based screening program for silent ischemia should be implemented in patients with diabetes. There are no convincing published data showing that a prospectively applied screening program improves outcomes in asymptomatic diabetic patients (71). However, there are certain attributes that increase the likelihood of silent ischemia being present and, thus, make screening more productive. In addition to advanced age, male gender, poorly controlled type 2 diabetes (elevated hemoglobin A1c), and the presence of retinopathy have been shown to correlate well with the presence of silent ischemia (72,73). Patients with two or more of these characteristics are reasonable candidates for screening for silent ischemia.

Acute Coronary Syndromes

MI rates are increased among diabetics of all ages (74). For example, in a population-based study by Haffner (75), the seven-year incidence of the first MI was 20% for diabetics but only 3.5% for nondiabetics. Prior history of MI increased the rate of recurrent MI and cardiovascular death in both groups (45% in diabetics and 18.8% in nondiabetics). Most importantly, in the absence of established CHD, diabetics experienced CHD morbidity and mortality at a rate equal to that of nondiabetic individuals with established CHD (20% vs. 18.8%, respectively). As a result, the NCEP now classifies diabetes as a CHD risk equivalent requiring aggressive intervention (12).

Diabetes worsens short- and long-term outcomes following acute MI, especially in women. The Framingham Study determined that the overall risk of cardiac mortality was two to four times higher in diabetics than in nondiabetics. Another study described one-month post-MI mortality rates of 14.4% in diabetic men and 21.7% in diabetic women compared with mortality rates of 8.8% and 7.8% in nondiabetic men and women, respectively. The subsequent one-year mortality of survivors was 9.6% for diabetic men and 10.7% for diabetic women compared with 5.0% and 2.5% for nondiabetic men and women, respectively (76). Diabetic patients had a 1.36 RR of death compared with nondiabetic patients in the SHOCK study, a trial of revascularization in MIs complicated by cardiogenic shock (77). In the GISSI-2 fibrinolytic therapy trial, the age-adjusted RR for mortality in diabetics was 1.4 for men and 1.9 for women (78).

Diabetes also appears to worsen the prognosis of unstable angina. In the six-nation Organization for the Advancement of Structured Information Standards (OASIS) registry of unstable angina and non-Q-wave MI, diabetes independently increased the risk of death by 57% (79). Fava et al. evaluated a group of 166 type 2 diabetics with unstable angina and compared them with 162 nondiabetic subjects. Diabetic patients experienced a greater than threefold increase in mortality at three months (8.6% vs. 2.5%) that was maintained at one-year (80).

The pathophysiologic explanation for the poorer prognosis among diabetic patients is not entirely clear. Diabetes is associated with complicated metabolic changes and alterations in coagulation parameters that may predispose to poorer outcome (81). Diabetic patients tend to have fewer collateral vessels compared with nondiabetics and may have more diffuse coronary disease (82). The poorer diabetic outcomes may also be partially explained by the observation that anterior infarction appears to be more common than inferior infarction. In one study involving 54 diabetic patients who had sustained an infarct compared with 270 nondiabetic MI patients, the incidence of anterior infarction was 43% in the diabetic group versus 13% in the comparison group (83). In a retrospective review of 147 patients with type 2 diabetes suffering a first MI in the drug and alcohol registry of treatment (DARTS), 37% of men had an anterior wall MI and 22% an inferior MI. Among women with type 2 diabetes this trend was reversed: 30% suffered
an inferior and 22% an anterior MI (84). Thus, it is not clear whether diabetes predisposes preferentially to anterior MI.

**Stroke**

The Framingham Study and others have demonstrated that the risk of stroke is increased 1.5 to 4 times for diabetic patients (85). Four case-control studies and five prospective observational cohort studies have also established that insulin resistance alone is associated with a 60% to 160% increased risk for stroke in nondiabetic patients (86). The risk of stroke is particularly increased in younger diabetic patients. In a study by Rohr et al. (87) involving 296 patients between the ages of 18 and 44, diabetes increased the odds ratio for stroke from a low of 3.3 for African-American women to a high of 23.1 for Caucasian men. In an Australian epidemiological study of stroke patients younger than 55 years, diabetes increased the risk of stroke over 10-fold, albeit with a wide confidence interval (odds ratio 11.6, 95% CI 1.2–115.2) (88).

Similar to post-MI prognosis, diabetes is also associated with a poorer prognosis after stroke. Diabetes increases the rate of stroke-related dementia by more than threefold (89). Diabetes also doubles the risk of stroke recurrence and increases stroke-related mortality (90,91). Poorer glycemic control also elevates stroke risk. In the Multiple Risk Factor Intervention Trial (MRFIT) of 347,978 men, those taking diabetes medications were three times more likely to incur a stroke (92).

Several clinical trials suggest that reducing insulin resistance and improving glycemic control may prevent cerebrovascular atherosclerosis and stroke. In 1998, the UKPDS group concluded that metformin was effective in preventing stroke based on a comparison of metformin therapy (n = 342) versus insulin or sulfonylurea therapy (n = 951). The metformin group not only achieved better glycemic control compared with the insulin/sulfonylurea group (hemoglobin Alc of 7.4% vs. 8.0%, respectively) but also achieved a lower stroke rate [12 stroke events in the metformin group (3.3 events/1000 patient-years) vs. 60 stroke events in the sulfonylurea/insulin group (6.2 events/1000 patient-years)] (40). Two other studies demonstrated that thiazolidinediones, compared with sulfonylurea therapy, are more effective in preventing carotid atherosclerosis in diabetic patients (93,94).

**Congestive Heart Failure and Left Ventricular Dysfunction**

The importance of diabetes as a risk factor for congestive heart failure (CHF) was first established in the Framingham Heart Study. Among participants between the ages of 45 to 75 years, the frequency of CHF was increased fivefold for diabetic women and 2.4-fold for diabetic men (95). Although the etiology for CHF in diabetics is often multifactorial (concomitant hypertension, ischemic heart disease, and/or microvascular disease), in the Framingham study, diabetes was a risk factor for CHF independent of coexisting hypertension or coronary artery disease.

Diabetes is observed in approximately 15% to 25% of heart failure patients in large clinical trials, and up to 30% of hospitalized heart failure patients have diabetes as a comorbid condition (96,97). In the large Assessment of Treatment with Lisinopril and Survival (ATLAS) and Studies of Left Ventricular Dysfunction (SOLVD) heart failure mortality trials (98,99) involving patients with systolic dysfunction, diabetes was identified as an independent predictor of death. In the SOLVD study diabetes was the third most important factor in predicting worsening heart failure after age and ejection fraction.
In a study of 9591 individuals with type 2 diabetes, independent risk factors for CHF included advanced age, diabetes duration, insulin use, ischemic heart disease, and elevated serum creatinine (100). These findings are supported by a recent population-based study of elderly patients with a mean age of 78.6 years, which concluded that diabetes is an independent risk factor for CHF and the risk of CHF increases with diabetes severity (101).

Although ischemic heart disease and hypertension contribute to the increased prevalence of CHF in diabetics, some diabetic patients develop heart failure in the absence of these conditions. Such patients with nonischemic diabetic cardiomyopathy present with heart failure associated with systolic and/or diastolic ventricular dysfunction (102). The histopathological changes observed in diabetic cardiomyopathy are usually indistinguishable from those of other nonischemic cardiomyopathies. Several mechanisms may contribute to the development of diabetic cardiomyopathy. Autonomic neuropathy manifested by either depletion of myocardial catecholamine stores (103) or impaired ventricular response to exercise due to sympathetic nervous system impairment (104) may play a role. A defect in glucose transporter (GLUT)4 receptor translocation to the cell surface in diabetic patients may interfere with myocardial energy metabolism (105). In addition, decreased insulin levels in type 1 diabetics and decreased insulin sensitivity in type 2 diabetics may reduce myocyte uptake of glucose via the GLUT4 receptor, which is insulin responsive (106).

The prevalence of left ventricular diastolic dysfunction is increased in the diabetic population, ranging from 27% to 70%. In large population-based studies, including the Strong Heart Study (107) and the Cardiovascular Health Study (108), relative to nondiabetics, echocardiograms of diabetic patients with no clinical history of heart failure demonstrated higher left ventricular mass, increased wall thickness, and greater arterial stiffness, all of which predispose diabetics to diastolic dysfunction. Diabetic patients may also have reduced systolic function at rest, lower ejection fractions with exercise (109), and reduced exercise tolerance despite well-controlled type 2 diabetes and hypertension (110).

Functional impairments in vascular reserve in the peripheral, coronary, and cerebral circulation have also been demonstrated in diabetic patients. Reduced coronary flow reserve and impaired vasomotor reactivity have been observed in patients with diabetes and angiographically normal coronary arteries, suggesting the presence of early endothelial dysfunction (111,112). These alterations in functional, rather than structural, coronary flow may account for the benefits of tight glycemic control and endothelial function-enhancing angiotensin-converting enzyme (ACE) inhibitors in the diabetic heart failure population. The importance of glycemic control in heart failure is illustrated by a large population-based study of 48,858 type 2 diabetic patients with no known history of heart failure who were followed for a mean of 2.2 years (113). After adjusting for multiple factors including age, sex, hypertension, alcohol consumption, duration of diabetes, and use of β blockers or ACE inhibitors, each 1% increase in glycosylated hemoglobin was associated with an 8% increased risk of heart failure. Conversely, after controlling for hypertension, age, and gender, heart failure appears to be a risk factor for the development of diabetes mellitus (114). During three-year follow-up of an elderly patient population, Scherer et al, demonstrated that the incidence of new-onset diabetes was 29% in heart failure patients, compared with 18% in subjects without heart failure (115).

**Autonomic Nervous System Dysfunction**

Diabetic autonomic neuropathy affects multiple organ systems including the gastrointestinal, neuroendocrine, genitourinary, and ocular systems. In a study of 120 asymptomatic
diabetic patients with no known history of coronary artery disease and normal 12-lead ECG, cardiovascular autonomic neuropathy (CAN) was present in 39% of the patients (116). In this study, the presence of CAN was also associated with an increased risk of subsequent major cardiac events, (8 out of 33 patients with CAN vs. 3 out of 42 in those without CAN; \( p = 0.04 \)). This finding may be explained by the observation that the parasympathetic system is affected earlier than the sympathetic system with a resultant relative increase in the sympathetic tone accompanied by elevated blood pressure and increased vasoconstriction.

Diabetic patients with autonomic nervous system dysfunction frequently present with orthostatic hypotension (fall in systolic blood pressure >20 mmHg lasting ≥3 min with a position change from supine to upright) and decreased exercise tolerance. Central and peripheral sympathetic denervation results in decreased splanchnic and peripheral vascular-bed vasoconstriction with resultant orthostatic hypotension. Diabetic postural hypotension can vary on a daily basis and may be exacerbated by insulin therapy and after meals (117). Decreased exercise tolerance is due to impaired sympathetic output with a resultant decrease in cardiac output. In advanced autonomic nervous system dysfunction, cardiac denervation can result in a fixed heart rate of 80 to 90 beats per minute (118). Sympathetic tone may be increased during the day and parasympathetic tone decreased at night, potentially increasing the risk for nocturnal arrhythmias (119).

Cardiac autonomic function can be assessed indirectly by cardiovascular reflex testing or directly by scintigraphic imaging. Cardiovascular reflex testing includes evaluation of both the sympathetic and parasympathetic systems by assessing heart rate variability with deep breathing, blood pressure response to handgrip and fall in systolic blood pressure with position changes (120). Scintigraphic imaging with metaiodobenzylguanidine or \( ^{11} \text{C}-\text{hydroxyephedrine} \) (both radiolabeled norepinephrine analogs that undergo uptake by the cardiac sympathetic nerve terminals) is more sensitive than reflex testing but not widely available.

Treatment of cardiovascular autonomic dysfunction includes lifestyle modifications, discontinuation of certain medications, and pharmacological therapy. Lifestyle modifications include a high-salt diet, small meals, avoiding alcohol and excessive heat, a 30° head-up tilt while sleeping, gradual changes in position, lower extremity compression stockings, and isometric exercises while upright (handgrip or “crossing leg” exercises). Potentially aggravating medications include diuretics, antihypertensives, and antidepressants. Pharmacological therapy includes fludrocortisone (mineralocorticoid), desmopressin (decreases vasopressin release), midodrine (\( \alpha \)-receptor agonist), pindolol (\( \beta \) blocker with intrinsic sympathomimetic activity), and octreotide (somatostatin analog). Elderly diabetic patients with orthostatic hypotension may be particularly difficult to treat since many such patients have comorbid conditions that require the administration of antihypertensive drugs and/or diuretics.

**Peripheral Arterial Disease**

Diabetic patients have a two- to fourfold increase in the incidence of PAD (121). In one study, patients with normal glucose tolerance had a 7% prevalence of abnormal ankle-brachial indices, while patients on multiple diabetic medications had a 20.9% prevalence of abnormal indices (122). Unlike microvascular disease, which is unique to diabetes, macrovascular disease manifesting as PAD is generally similar in diabetics and nondiabetics and is the result of accelerated atherosclerosis. However, some clinical differences exist in diabetic PAD: (i) The disease is more likely to involve the infrapopliteal arteries of the lower extremities (123); (ii) claudication is more common in
diabetics (3.5-fold risk in men and 8.6-fold risk in women) (124,125); and (iii) amputation is much more frequent in diabetics, especially in older diabetics. The 12.7 (95% CI, 10.9–14.9) RR of lower extremity amputation in diabetic versus nondiabetic patients increases to 23.5 (95% CI, 19.3–29.1) in diabetics 65 to 74 years old (126). Both the incidence and extent of the disease are directly associated with the duration and severity of diabetes.

MANAGEMENT OF CARDIOVASCULAR DISEASE IN PATIENTS WITH DIABETES MELLITUS

Acute Coronary Syndromes

Few studies have addressed specifically the impact of modern medical therapies for acute coronary syndromes (ACS) in the diabetic population. Subgroup analyses, however, of several clinical trials suggest a generally consistent beneficial effect of modern therapies in diabetic patients. The management of ACS is similar for elderly patients with and without diabetes with few exceptions, as noted below. Four major issues will be considered here: (i) optimal reperfusion therapy for ST-elevation MI (STEMI); (ii) early invasive versus early conservative management of unstable angina and non–ST-elevation MI (UA/NSTEMI); (iii) adjunctive pharmacotherapy and its applicability to the elderly diabetic patient with ACS; and (iv) glycemic control in patients with ACS.

Reperfusion Therapy for STEMI

Thrombolytic therapy. Thrombolytic (TL) therapy for STEMI has been shown to be equally or more beneficial in the diabetic patient compared with the nondiabetic. The Fibrinolytic Therapy Trialists (FTT) overview found a statistically greater mortality benefit in the diabetic group: 37 lives saved per 1000 patients treated compared with 15 lives saved per 1000 treated patients among nondiabetics (127). Similarly, an angiographic analysis that included 310 patients with diabetes in a Global Utilization of Streptokinase (GUSTO) I substudy demonstrated comparable infarct-related artery patency at 90 minutes after TL therapy in patients with and without diabetes (128). Concerns about possible increased ocular hemorrhagic complications because of underlying diabetic retinopathy have not been substantiated (129). The beneficial effects of TL in the very elderly (>75 years of age) are uncertain. The original FTT overview showed no statistically significant survival benefit in patients over the age of 75 years, possibly due to an increased incidence of hemorrhagic stroke. However, reanalysis of the FTT data showed that among patients treated within six hours of the onset of STEMI, mortality was significantly reduced in patients over 75 years of age, and the absolute benefit was similar to that seen in patients 55 to 74 years of age (130). Conversely, two more recent population-based analyses suggest that short-term mortality from STEMI is not reduced and may even be increased in patients over 75 years who receive TL therapy (131,132). Thus, the use of this form of reperfusion therapy in very elderly patients with and without diabetes remains controversial. For patients up to age 75, however, there is clear evidence from multiple randomized controlled trials that TL therapy affords a significant survival benefit.

Primary percutaneous coronary intervention. Acute success rates with primary percutaneous coronary intervention (PPCI) are comparable in the presence or absence of diabetes, although the restenosis and long-term mortality rates are higher in diabetic patients (133,134). Despite the well-known limitations of PPCI (lack of widespread
availability and treatment delays), accumulating evidence suggests that this form of reperfusion therapy may well be superior to TL in improving clinical outcomes if performed expeditiously by experienced operators (135). Data comparing TL with PPCI in elderly diabetic patients are limited. A recent observational study comparing early and late outcomes of PPCI and TL therapy of diabetic patients with STEMI concluded that PPCI was associated with reduced early and late adverse outcomes when compared with TL therapy (136). However, mortality was similar in both groups. In this study over one-third of the patients were 65 years or older.

The advent of stents has bolstered the role of PPCI as the reperfusion treatment of choice in acute STEMI. In the Controlled Abciximab and Device Investigation to Lower Late Angioplasty Complications (CADILLAC) trial, routine stent implantation in diabetic patients with an acute STEMI significantly reduced restenosis and improved survival free from subsequent target vessel revascularization. Despite these improved outcomes with stenting in patients with diabetes, one-year mortality was significantly higher in diabetic patients who received stents compared with nondiabetics (8.2% vs. 3.6%; \( p = 0.005 \)) (137). On the basis of available data, it is reasonable to conclude that PPCI is preferable to TL in the elderly diabetic patient with STEMI, including those over the age of 75.

**Management of UA/NSTEMI**

Beginning with the Thrombolysis in MI (TIMI) III study of early invasive versus early conservative management of UA, subgroup analyses of several randomized controlled trials have demonstrated a consistent, modest benefit of early invasive therapy in elderly patients (aged \( > 65 \) years) and in diabetics. In the Fast Revascularization During Instability in Coronary Artery Disease (FRISC) II trial (138), reduction in the composite endpoint of death and nonfatal MI among those assigned to the early invasive group resulted entirely from the benefit realized by the subgroup over age 65. The five-year outcomes of the FRISC II trial showed sustained benefits in favor of the invasive strategy for the primary endpoint of death or nonfatal MI (19.9% in the invasive arm vs. 24.5% in the noninvasive arm). This benefit was confined to nonsmokers and male patients with two or more risk indicators (aged \( > 65 \) years, diabetes mellitus, ST-segment depression, and elevated troponin level on admission) (139). The more recent TACTICS-TIMI 18 study compared outcomes of ACS patients treated with the glycoprotein IIb/IIIa (GP IIb/IIIa) inhibitor tirofiban and assigned to either an early invasive strategy and revascularization if clinically indicated or to a more conservative strategy in which cardiac catheterization was undertaken only if the patient demonstrated spontaneous or provoked ischemia (140). Although there was no clear survival benefit, the results demonstrated a 3.1% absolute and 33% RR reduction for the combined endpoint of death, nonfatal MI, and rehospitalization for ACS at six months in patients assigned to an early invasive strategy. Subgroup analysis demonstrated that patients over the age of 65 years had a 4.6% absolute reduction in the combined endpoint compared with a 2.9% reduction for patients under the age of 65. Similarly, diabetic patients realized a 7.6% absolute reduction compared with 2.2% for nondiabetic patients. On the basis of these and other trials, an early invasive strategy is considered to be the preferred method of managing “high-risk” patients with UA/NSTEMI. Since both advancing age and diabetes increase the risk of adverse outcomes, it is reasonable to conclude that an early invasive strategy is appropriate in the elderly diabetic patient with UA/NSTEMI. An important limitation of these studies, however, is that very few diabetic patients over the age of 80 were enrolled (141).
Adjunctive Therapies in ACS

In almost all respects, the adjunctive therapy of ACS is the same for patients with and without diabetes mellitus (142). However, specific contraindications and risks must be recognized as discussed below.

Aspirin. The beneficial effects of aspirin in ACS have been conclusively demonstrated in many studies. In the International Study of Infarct Survival ISIS-2 study, aspirin was shown to be as efficacious in older as in younger patients with MI (143). Several studies have shown that patients with either type 1 or type 2 diabetes mellitus have a prothrombotic state including enhanced platelet aggregation in response to various stimuli (144,145), and that agents that inhibit platelet aggregation in vivo consistently reduce the incidence of thrombotic events. In a meta-analysis of 145 prospective controlled trials of antiplatelet therapy after an MI, stroke, or transient ischemic attack reported by the Antiplatelet Trialists (146), antiplatelet therapy was associated with a reduction of about 25% in vascular events, and diabetic patients had risk reductions similar to nondiabetic individuals. Consequently, aspirin in doses of 162 to 325 mg should be administered to all patients with ACS and should be continued indefinitely if there are no major contraindications (e.g., bleeding peptic ulcer).

Other antiplatelet therapy. Platelet aggregability is enhanced in patients with diabetes mellitus. Several studies have shown that GP IIb/IIIa inhibitors, when added to aspirin, improve outcomes in high-risk patients with UA/NSTEMI, especially those undergoing percutaneous coronary intervention (PCI). A review of the results of four abciximab trials (147) reveals that this agent is safe and effective in patients over the age of 70, although the net benefit declines slightly with increasing age. Tirofiban and eptifibatide have also been shown to be effective agents in this setting. In a meta-analysis by Roffi et al. of six large randomized ACS trials involving 6458 patients with and 23,072 patients without diabetes and in which immediate PCI was not mandated, benefits from GP IIb/IIIa inhibitors were seen mainly among patients with diabetes, in whom 30-day mortality was reduced by 26%, from 6.2% to 4.6% \((p = 0.007)\). Even more striking was the benefit of GP IIb/IIIa inhibitors among diabetic patients undergoing PCI. In this subgroup, 30-day mortality was reduced by 70%, from 4.0% to 1.2% (148). It is not clear whether this preferential benefit in diabetics is related to diabetes-associated conditions such as increased platelet activation and accentuated inflammatory responses, or is because of the more diffuse atherosclerotic process of diabetes. Nevertheless, routine use of these agents is recommended for moderate- and high-risk diabetic patients with ACS.

Clopidogrel was shown in the Clopidogrel in Unstable Angina to Prevent Recurrent Ischemic Events (CURE) trial to improve long-term outcomes when administered for three to nine months to patients with UA/NSTEMI who did not undergo PCI (149). Improved outcomes were demonstrated in patients over the age of 65 years and in patients with diabetes mellitus. However, diabetic patients derived only a modest benefit from combined aspirin/clopidogrel therapy at 3 to 12 months, with a composite death, an MI, or a stroke rate of 14.2% versus 16.7% \((p = ns)\). In patients undergoing PCI (PCI-CURE study), combined aspirin/clopidogrel therapy conferred a slightly lower benefit in diabetic patients (absolute risk reduction 3.6% compared with 3.8% in nondiabetics) (150). Similar results were obtained in the more recent Clopidogrel for the Reduction of Events During Observation (CREDOS) trial in which the benefit from pretreatment/sustained clopidogrel therapy in 560 diabetic patients was again modest compared with that observed among the 1556 nondiabetics (RR reduction 11% and 33%, respectively for the
primary composite endpoint of death, MI, and stroke at one year) (151). Nevertheless, sufficient benefit is obtained from combined aspirin/clopidogrel therapy in diabetic ACS patients to suggest that it should be administered to all such patients unless contraindicated.

The use of triple antiplatelet therapy (aspirin-clopidogrel-GP IIb/IIa inhibitors) in elderly diabetic ACS patients has raised concerns because of the increased risk of bleeding. Despite these concerns, results obtained in diabetic patients undergoing PCI and receiving triple antiplatelet therapy in the TARGET (152) and other trials suggest that such therapy is probably warranted in elderly diabetic patients with ACS unless major contraindications exist. Data for patients 80 years and older is sparse due to enrollment bias in almost all studies (141).

**Antithrombotic therapy.** Intravenous unfractionated or low-molecular-weight heparin (LMWH) should be administered to all patients with ACS regardless of age and diabetic status unless there are major contraindications (e.g., intracranial bleed). Recent studies have shown that LMWH is superior to unfractionated heparin in patients with UA/NSTEMI, especially in elderly patients (153,154). Concerns regarding excess bleeding when patients receiving LMWH undergo an invasive procedure have not been substantiated.

**β-Adrenoreceptor blockers.** β Blockers have been found to be effective in improving outcomes when used for ACS in patients with diabetes. Several studies have consistently demonstrated an average twofold greater reduction in the RR of mortality as a result of β-blocker therapy after MI in patients with diabetes compared with those without diabetes. Despite these findings, diabetics with coronary artery disease are undertreated with β-blocker drugs. Reviewing a large cohort of patients from the National Cooperative Cardiovascular Project, Chen et al. reported that even after adjusting for demographics and clinical factors, patients with diabetes were less likely to receive β blockers at discharge following acute MI, with odds ratios for insulin-treated and non-insulin-treated diabetics of 0.88 and 0.93, respectively (155). In the same study, β blockers were found to be associated with lower one-year mortality for insulin-treated diabetics, non-insulin-treated diabetics, and nondiabetics (hazard ratios 0.87, 0.77, 0.87, respectively). Furthermore, β-blocker therapy was not significantly associated with increased six-month readmission rates for diabetic complications. The authors concluded that β-blocker therapy following acute MI is associated with similar reductions in one-year mortality rates for elderly diabetic and nondiabetic patients without increasing the risk of diabetic complications. Subgroup analysis of several large β-blocking trials has shown a 30% to 58% reduction in post-MI mortality in diabetic patients treated with timolol (156) or metoprolol (157). In the more recent Effect of Carvedilol on Outcome after MI in Patients with Left Ventricular Dysfunction (CAPRICORN) trial, all-cause mortality was reduced from 15% in the placebo group to 12% in the carvedilol group (RR reduction 23%; p = 0.031) (158). The benefit derived from carvedilol was equal in patients under or over age 70. Patients with diabetes also derived benefit, although to a lesser extent than nondiabetics. On the basis of these and other studies, β blockers should be used in all elderly diabetic patients with ACS in the absence of major contraindications (severe bradycardia with heart rate <45–50 beats/min, systolic blood pressure <100 mmHg, severe heart failure, PR interval >0.24 seconds or higher degrees of atrioventricular block, and active bronchospastic lung disease).

**ACE inhibitors.** Early treatment with an ACE-I is recommended for patients with an anterior STEMI, left ventricular systolic dysfunction with an ejection fraction of less than
Diabetes Mellitus and Cardiovascular Disease in the Elderly

0.4, or overt heart failure in the absence of contraindications such as hypotension, renal insufficiency, or hyperkalemia (159–161). These agents are beneficial in other forms of ACS as well, but the evidence is less compelling. Despite the generally recognized benefits of ACE-I in diabetic patients, these agents are under-prescribed because of concerns regarding azotemia, hemodynamic instability (especially if diabetes-related autonomic neuropathy is present), and hyperkalemia. However, results from multiple studies do not support these concerns. A retrospective analysis of the GISSI 3 study suggests that most, if not all, of the mortality benefit resulting from treatment with lisinopril versus placebo was found in the diabetic subgroup (162). In the CONSENSUS II study, hypotension neutralized any potential benefit of early ACE inhibition in ACS patients treated with intravenous enalaprilat, but in the diabetic subgroup, those receiving enalaprilat exhibited a significant improvement in outcomes at six months compared with placebo (163).

The Heart Outcomes Prevention Evaluation (HOPE) trial investigated the effect of ramipril versus placebo in 9297 high-risk patients 55 years of age or older with evidence of vascular disease or diabetes plus one other cardiovascular risk factor and without left ventricular dysfunction or heart failure (164). Patients with diabetes constituted 38% and 39% of the treatment and placebo groups, respectively. Ramipril was found to significantly reduce the risk of MI, stroke, or death from cardiovascular causes compared to placebo. The beneficial effect of treatment with ramipril on this composite outcome was consistently observed in patients with or without diabetes mellitus and was independent of age. Thus, the HOPE trial confirms results of prior studies regarding the benefits of ACE-I in diabetic patients.

Glycemic Control in ACS

Hyperglycemia is associated with multiple deleterious biochemical changes including increased activation of both inflammatory and thrombotic pathways, increased oxidative stress, and microcirculatory effects including reduced vasodilation in response to ischemia, decreased response to vasodilators, reduced coronary collateral blood flow, and reduced nitric oxide synthesis (165,166). These changes adversely impact outcomes in ACS. Conversely, insulin has anti-inflammatory and antithrombotic activity, and acts as a vasodilator and inhibits platelet activation (167). One would, therefore, expect that in diabetic patients with ACS, tight glycemic control and/or insulin administration might improve outcomes.

Twenty nine trials and meta-analyses investigating the role of insulin treatment [administered either for tight glycemic control or as a component of glucose-insulin-potassium (GIK) regimens] in patients with ACS or undergoing cardiac surgery have been published since the year 2000 (168). Conflicting results have been reported and, in general, the trials are difficult to interpret because of heterogeneity of the study populations and the treatment regimens. Therefore, despite some studies demonstrating a modest survival benefit in diabetic patients with ACS treated with GIK (169), the overall evidence suggests that the use of GIK is probably not beneficial (168). On the other hand, substantial data support the aggressive treatment of diabetes with insulin at the time of an acute illness including ACS both in terms of improving short-term outcomes and for preventing long-term cardiovascular and microvascular complications (170–173). A recently proposed paradigm of care for managing NSTEMI, known as the “ABCDE” approach, emphasizes the importance of diabetes management (the “D” in “ABCDE”) in the setting of ACS (174).

Recently, Swedish investigators reported that in diabetic patients with ACS, hyperglycemia on arrival to the hospital and hypoglycemia during hospitalization were
both independently associated with worse adjusted all-cause mortality risk (175). The authors concluded that avoidance of both hyper- and hypoglycemia during ACS events is important, and that proper glycemic control is a major objective of ACS care. Despite the theoretical and clinical evidence pointing to the importance of glycemic control in ACS patients, management of diabetes in this setting is frequently suboptimal. A recent study found that almost one-third of 235 diabetic patients admitted with ACS did not have an assessment of HbA1c during hospitalization or at discharge, particularly older patients and those not evaluated by an endocrinologist. In addition, only 42% of patients with HbA1c levels of 7% to 9% had their diabetic medications adjusted (176).

**Chronic Ischemic Heart Disease**

The medical management of chronic ischemic heart disease and stable angina pectoris is the same for elderly patients with and without diabetes. In the absence of contraindications, all patients with stable angina should be treated with aspirin, a β blocker, an ACE inhibitor or angiotensin receptor blocker (ARB), and a statin. Additional drugs that may be indicated in selected cases include long- and short-acting nitrates, calcium channel blockers, ranolazine, and clopidogrel. There is agreement that the presence of diabetes does not require a change in the pharmacotherapy of stable angina, nor is there compelling evidence that these drugs have untoward effects in diabetics.

**Management of Silent Ischemia**

The proper management of the elderly diabetic patient with silent ischemia starts with lifestyle modification and aggressive medical therapy of the commonly associated hypertension and hyperlipidemia, as is true for all diabetics. There is evidence that agents that are used to treat symptomatic ischemia (β blockers, calcium antagonists, and nitrates) also effectively reduce or eliminate episodes of silent myocardial ischemia (177,178). However, there is no evidence that anti-ischemic medical therapy can alter the natural history of CHD in these patients. Coronary revascularization is also effective in reducing or eliminating episodes of silent ischemia. In the Asymptomatic Cardiac Ischemia Pilot (ACIP) trial, 57% of patients randomized to revascularization were free of ischemia at one year compared with 31% in the ischemia-guided strategy group (179). In the recently reported Swiss Interventional Study on Silent Ischemia Type II (SWISSI II) randomized study on the effects of PCI in patients with silent ischemia following an MI, an absolute reduction of 6.3% in major cardiac events (cardiac death, recurrent MI, and/or symptom-driven revascularization) was recorded for the PCI group compared with the anti-ischemia drug therapy group (180). It is not clear whether the results of this study can be applied to elderly diabetic patients with silent ischemia since the mean age of enrolled patients was 54.4 years in the PCI group and 56.2 years in the medical therapy group. Similarly, only 9.4% of PCI patients and 13.3% of medical therapy patients had documented diabetes. Nevertheless, the practice of referring diabetic patients with silent ischemia and high-risk noninvasive test results to coronary angiography and revascularization seems reasonable (181).

**Revascularization Therapy**

Almost 25% of the surgical and percutaneous coronary revascularization procedures performed annually in the United States are in patients with diabetes. Most of these patients have comorbid conditions that contribute to worse short- and long-term outcomes after revascularization. These comorbidities include hypertension, dyslipidemia, systolic
and diastolic left ventricular dysfunction, PAD, cerebrovascular disease, nephropathy, and a prothrombotic state.

Acute success rates of percutaneous transluminal coronary angioplasty (PTCA) are similar for patients with and without diabetes. However, the incidence of restenosis, the need for repeat revascularization, and long-term mortality after PTCA are higher in diabetic patients. Data from the National Heart, Lung, and Blood Institute (NHLBI) registry indicated that the nine-year mortality of diabetic patients after PTCA was almost double than that for nondiabetics (182). Such data have raised the possibility that coronary artery bypass graft surgery (CABG) may be advantageous in diabetic patients.

The Bypass Angioplasty Revascularization Investigation (BARI) trial compared the two types of revascularization therapy in patients with two- or three-vessel disease. The overall five-year survival rates of 89.3% in the CABG group and 86.3% in the angioplasty group were not statistically different (183). However, in the subgroup of BARI patients with treated diabetes mellitus (not a prespecified subgroup), a significant difference was observed in favor of bypass surgery (survival of 76% for CABG vs. 56% for PTCA; \( p = 0.0011 \)) (184). Improved five-year survival in CABG patients was entirely due to reduced cardiac mortality (5.8% vs. 20.6%; \( p = 0.0003 \)). Improved survival with bypass surgery in treated diabetics was confirmed at seven-year follow-up of the BARI trial (185). It should be noted, however, that the survival advantage of CABG was largely confined to patients who received at least one arterial conduit.

The results of the BARI trial could not be confirmed in the Emory Angioplasty versus Surgery Trial (EAST) or the Duke Cardiovascular Registry (186,187). However, a more recent analysis of the EAST data suggests that, after accounting for baseline differences between groups, there was a higher long-term mortality rate for diabetic patients treated with angioplasty compared with those undergoing CABG (188). Several possible mechanisms have been proposed for the higher mortality rate after PTCA in insulin-requiring patients with diabetes: impaired endothelial function, a prothrombotic state, increased intimal hyperplasia, and increased protein glycosylation and vascular matrix deposition. Alternatively, insulin-requiring diabetes may be a marker for more severe disease and may identify patients for whom surgery is a better option than angioplasty.

A limitation of both BARI and the Duke Registry is that neither study included a significant number of patients treated with intracoronary stents or GP IIb/IIIa inhibitors. These treatment modalities have improved the outcomes of PCI in diabetics as well as in nondiabetics. Evaluation of Platelet IIb/IIIa Inhibitors for Stenting Trial (EPISTENT) was a randomized study of patients with at least one coronary artery stenosis more than 60%. Patients were randomized into three treatment groups: stenting plus standard therapy and placebo, stenting plus standard therapy and abciximab, and conventional angioplasty plus standard therapy and abciximab. First generation bare metal stents (BMS) were used in this study. Subgroup analysis centered on 491 patients with diabetes mellitus (189). In this cohort, an approximately equal number of patients were assigned to each of the treatment arms, and baseline characteristics were similar in the three groups. Endpoints were six-month death, MI, and target vessel revascularization. In the diabetic patient cohort, a significant reduction in the combined endpoint was noted in the group treated with the combination of stenting and abciximab. An absolute reduction of events and increased benefit for all endpoints was observed in the stent/abciximab group compared with the two other treatment groups. After multivariate analysis to adjust for some imbalance of baseline clinical and angiographic findings, the benefit of stent/abciximab in diabetics remained significant (\( p = 0.008 \)).

Recent studies have provided evidence that drug-eluting stents (DES) may be superior to BMS in patients with and without diabetes. Two meta-analyses of randomized,
controlled trials concluded that DES substantially reduced restenosis and target vessel revascularization compared with BMS (190,191), although short-term mortality was not different. However, data from diabetes subgroups in randomized controlled trials indicate that the rate of restenosis in diabetics treated with DES is still significantly greater than in nondiabetics (192,193). Recently reported meta-analyses of randomized trials evaluating the safety of DES have raised new serious questions and are particularly of concern regarding the use of DES in diabetic patients. One study reported a trend of increased incidence of late (after one year) DES thrombosis compared with BMS (194). A second reported a significantly better four-year survival of diabetic patients treated with BMS (95.6%) compared with patients treated with DES (87.8%; \( p = 0.008 \)) (195). Therefore, it is clearly premature at this point to consider DES a viable revascularization alternative to CABG for diabetic patients with multivessel CHD (196,197).

This conclusion is supported by several recent small trials that have reported results similar to the BARI trial. In the Brazilian Medicine, Angioplasty, or Surgery Study (MASS), diabetic patients (mean age 60 ± 9 years) with multivessel CHD had better five-year outcomes after CABG compared with patients who underwent PCI or were treated medically (198). In another study from Israel, 518 consecutive diabetic patients (29% over the age of 70) underwent revascularization, 176 by PCI incorporating the use of Cypher stents and 342 by CABG. Left main disease, total occlusion of a coronary artery, and bifurcation lesions were more prevalent in the surgical group. During a mean follow-up of 18 months, overall mortality was not different in the two groups, but recurrent angina and repeat intervention were more common in the PCI group (199). It is noteworthy that despite the reported worsening of surgical case mix, CABG is being performed in diabetic patients with low morbidity and mortality rates that are fairly comparable with those of nondiabetics. In a retrospective report from the Bristol Royal Infirmary (200) of 5259 patients undergoing CABG, the in-hospital mortality for the diabetic cohort was 2.2% compared with 1% for nondiabetic patients.

Currently, the 2005 Update of the American College of Cardiology/American Heart Association (ACC/AHA) PCI Guidelines gives a class IIb recommendation (efficacy not well established) for PCI in patients with diabetes, class III angina, and two or three vessel CHD including significant left anterior descending artery disease (201). Two ongoing trials [BARI 2D and Future Revascularization Evaluation in Diabetic Patients: Optimal Management of Multivessel Disease (FREEDOM)] should help clarify the role of PCI using modern stent deployment and appropriate antiplatelet regimens in patients with diabetes and multivessel CHD.

HYPERTENSION AND DIABETES MELLITUS

Patients with diabetes have an increased prevalence of hypertension (202) and, conversely, hypertensive patients have an increased incidence of impaired glucose tolerance and demonstrate increased insulin release following an oral glucose load. The results of several studies support the existence of the metabolic syndrome that includes insulin resistance and hyperinsulinemia, glucose intolerance, hypertension, obesity, elevated triglycerides, and other metabolic abnormalities (203). More than seven million people in the United States have both hypertension and diabetes, and the association between these risk factors and cardiovascular disease becomes stronger with advancing age. Epidemiological studies have demonstrated that hypertension increases the risk of atherosclerotic vascular disease in diabetics more than in nondiabetics. The Systolic Hypertension in the Elderly Program (SHEP) found almost twofold increases in the five-year rates of major cardiovascular events, coronary events, and
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strokes among diabetic patients versus nondiabetic patients in the placebo group (204). The relative treatment benefit of low-dose diuretic therapy was similar in patients with diabetes compared with nondiabetic patients, but the absolute benefit was lower in patients with diabetes. The SHEP trial results refuted the belief that diuretics, which may increase blood glucose levels, must be avoided in patients with diabetes. Similar salutary effects of thiazide treatment in diabetic patients with hypertension were seen in the Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack (ALLHAT) trial, in which over 35% of the patients had type 2 diabetes (205). In general, the drugs commonly used to treat hypertension (β blockers, calcium channel blockers, ACE inhibitors, and diuretics) are effective in patients with diabetes (206). Thiazide diuretics in high doses can indeed aggravate hyperglycemia, but at lower doses—which are equally effective in treating hypertension—they do not significantly increase glucose intolerance. Similarly, although β blockers may worsen insulin resistance and mask symptoms of hypoglycemia, they are generally well tolerated by patients with diabetes and are especially indicated if there is associated CHD.

Systolic hypertension is especially common in the elderly because of the age-related decline in compliance of the central elastic arteries. The increase in systolic pressure, in turn, results in an increase in pulse pressure (PP). Factors other than age that promote an increase in vascular stiffness and that are associated with a widened PP include tobacco, diabetes, glucose intolerance, and hyperlipidemia (207,208). The Cardiovascular Health Study found that increased PP was associated with a 21% increased risk of cardiovascular events for each progressive standard deviation increase above the mean (209). Even though a widened PP is now recognized as a risk factor for future cardiovascular events, reduction of PP has not been an endpoint in hypertension trials, and treatment goals have centered on reduction of systolic blood pressure (210). The important relationship between diabetes and BP is underscored in the Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure (JNC-7) (206), which sets the target for BP control for diabetics to less than 130/80 mmHg compared with the target for the general population of less than 140/90 mmHg.

In the large multicenter randomized UKPDS trial, one objective was to determine whether tight control of hypertension with either a β blocker or an ACE-I was beneficial relative to standard care (211). Patients were randomly assigned to captopril or atenolol for control of hypertension. The study concluded that both agents were equally effective in reducing blood pressure as well as the risks of microvascular endpoints. Regarding macrovascular complications of diabetes, although reductions in all-cause mortality and MI did not achieve statistical significance, there was a 44% reduction of stroke and a 56% reduction of heart failure in the tight blood pressure control group compared with the conventionally treated group. Thus, aggressive therapy of hypertension in diabetic patients is crucial, but the choice of antihypertensive agent appears to be less important unless there is a specific indication for one class of drug over another. ACE-I and ARBs have been shown to slow progression of diabetic nephropathy and may, therefore, be the preferred initial agents in the presence of microalbuminuria. Similarly, β blockers are the preferred agents in patients with angina or MI. Most elderly diabetic patients with hypertension will require more than one antihypertensive drug for optimal blood pressure control (206).

LIPID DISORDERS AND DIABETES MELLITUS

Patients with diabetes mellitus commonly have two lipid disorders that must be considered. The first is an elevated low-density lipoprotein (LDL) cholesterol level. This leads to atherogenesis and contributes to plaque rupture and acute coronary events. The
second is atherogenic dyslipidemia, which is characterized by increased triglyceride levels, depressed high-density lipoprotein levels, and normal to mildly increased low-density lipoprotein levels but increased levels of small dense (easily oxidizable) LDL particles. Both these disorders are independently associated with progressive atherosclerosis and increased incidence of cardiovascular events (212, 213).

The importance of controlling both of these diabetes-associated lipid disorders and the impact of such control on the macrovascular complications of diabetes have been extensively studied. In 1992, the Helsinki Heart Study suggested a trend toward decreased coronary events in 135 diabetic patients treated with gemfibrozil over a five-year period, compared with those receiving placebo (214). Because of concerns regarding the efficacy and safety of fibrate therapy, this form of treatment has not gained wide acceptance. However, the more recent Diabetes Atherosclerosis Intervention Study (DAIS) has provided support for the use of fibrates in the treatment of diabetic dyslipidemia (215). DAIS was a randomized trial designed to assess the effects of correcting lipoprotein abnormalities on coronary atherosclerosis in type 2 diabetes. Patients were assigned to micronized fenofibrate or placebo and followed for at least three years. In addition to improved lipid profiles, the fenofibrate-treated patients were shown to have significantly less angiographic progression of coronary artery disease compared with the placebo group. The study was not powered to assess clinical endpoints, but there were fewer events in the fenofibrate group than in the placebo group.

Recently, attention has been focused on the fundamental role inflammatory processes play in the initiation, propagation, and complications of atherosclerosis (216), and the role of peroxisome proliferator-activated receptors alpha and gamma (PPAR-α and PPAR-γ) in the control of inflammation and cardiovascular risk (217). Gemfibrozil and fenofibrate are PPAR-α agonists that significantly lower triglyceride levels while modestly raising HDL cholesterol (215). In the Fenofibrate Intervention and Event Lowering in Diabetes (FIELD) study of 9795 patients with type 2 diabetes, fenofibrate therapy resulted in a nonsignificant 11% reduction in the primary endpoint of CHD death or nonfatal MI ($p = 0.16$). However, a 25% reduction in coronary events ($p = 0.014$) was recorded in the subgroup of patients who entered the study without prior history of CHD (218). The results of the FIELD study are confounded by unequal initiation of statins in the two groups during the study, and by the mix of low-risk primary and medium-risk secondary prevention patient cohorts. Nevertheless, the FIELD study is important because it demonstrated a generally good safety profile for combined statin-fenofibrate therapy; in addition, fenofibrate therapy was associated with unexpected benefits on microvascular endpoints (microalbuminuria and retinopathy). In the Veterans Affairs High Density Lipoprotein Intervention Trial (VA-HIT), gemfibrozil reduced the risk of major cardiovascular events by 24% ($p < 0.001$). In this study, 25% of the subjects had diabetes and most had the characteristics of the metabolic syndrome. Furthermore, the clinical benefit of gemfibrozil exceeded that attributable to changes in the lipid profile (219); this finding suggests that the cardiovascular protection provided by fibrates may be mediated in part by the anti-inflammatory actions induced by PPAR-α activation.

Although the results of the fibrate studies are inconclusive in terms of clinical outcomes, subset analysis of diabetic patients in three major secondary prevention trials comparing HMG CoA-reductase inhibitors (statins) with placebo demonstrate the importance of LDL cholesterol control in diabetics. The Scandinavian Simvastatin Survival Study (4S) showed that in a subgroup of 202 diabetic patients, simvastatin led to a significant reduction in major coronary artery disease events over a five-year follow-up period compared to placebo (220). The Cholesterol And Recurrent Events (CARE) trial enrolled 586 diabetic patients and also reported a significant reduction in major coronary
events when pravastatin was compared with placebo (221). The Long-Term Intervention with Pravastatin in Ischemic Disease (LIPID) trial enrolled 811 patients with diabetes and reported a favorable trend in the composite endpoint of CHD death or nonfatal MI over an average follow-up of six years among patients treated with pravastatin compared with placebo (222). Similar results in diabetic patients were seen in the more recent Heart Protection Study (HPS) (223) and the Collaborative Atorvastatin in Diabetes Study (CARDS) (224). The HPS demonstrated benefits from statin therapy even in patients with baseline LDL cholesterol levels less than 100 mg/dL. Subgroup analyses from the HPS, LIPID, and 4S trials showed that older individuals derived equal or greater benefit from statin therapy than younger patients.

Ezetimibe is a novel lipid-lowering agent that inhibits cholesterol absorption by a unique mechanism of action. The addition of ezetimibe to a statin has been shown to result in significant additional LDL-C lowering. The Ezetimibe Add-On to Statin for Effectiveness (EASE) trial was designed to determine the effects of combination therapy on LDL-C reduction and NCEP ATP III goal attainment in a diverse population of patients. The addition of ezetimibe to a statin regimen reduced LDL-C by 25.8% ($p < 0.001$) below the LDL-C level of statin monotherapy (225). More than half of the patients had metabolic syndrome or diabetes mellitus and the dual regimen was well tolerated. Thus, a combined regimen of statin-ezetimibe can be used successfully in diabetic patients who fail to achieve LDL-C goals with statin monotherapy. No information is available regarding the safety and efficacy of triple hypolipidemic therapy (e.g., statin-ezetimibe-fenofibrate) (226).

Despite the limited information that has emerged from primary prevention trials, strong evidence from secondary and some primary prevention studies indicates a definite role for lipid-altering therapy in patients with diabetes mellitus. The 4S trial showed that simvastatin treatment had a greater effect on endpoint reduction in the subgroup with diabetes than in the nondiabetic group (220); similarly, in the HPS, simvastatin reduced major coronary events and strokes in diabetic subjects with one other risk factor but no known vascular disease to the same extent as in other high-risk subjects without diabetes (223). On the basis of currently available evidence derived from multiple prospective randomized trials, statins remain the agents of first choice for the treatment of older patients with hyperlipidemia and type 2 diabetes, with the possible addition of ezetimibe to achieve NCEP Adult Treatment Panel (ATP) III goals. Fenofibrate is a reasonable second-line agent, especially for those diabetics with atherogenic dyslipidemia (high triglycerides and low HDL levels). The precise role of combined statin-fibrate therapy for cardiovascular risk reduction in patients with type 2 diabetes is under investigation in the ongoing Action to Control Cardiovascular Risk in Diabetes (ACCORD) trial. Several studies have reported an increased incidence of myopathy when gemfibrozil is added to a statin and this combination is best avoided (226).

Niacin has beneficial effects on total cholesterol, LDL-C, and triglycerides; it also effectively raises HDL cholesterol levels, and in combination with low-dose statin therapy it retards the progression of CHD and reduces the occurrence of major cardiac events (227). The side effects of niacin, which include cutaneous flushing, hepatic toxicity, and induction of insulin resistance have limited its use in general clinical practice. However, the problem of flushing can be addressed with good patient education and the administration of aspirin 30 to 60 minutes before niacin intake. Serious hepatic toxicity is largely confined to the use of slow-release formulations; nevertheless careful monitoring of hepatic function is necessary in all patients taking this drug. Although niacin has been shown, in short-term trials, to induce insulin resistance, the glycemic response in patients with and without diabetes is usually minor. Thus, niacin can be used
safely in selected patients with diabetes provided careful monitoring of the various metabolic parameters is observed (228).

TREATMENT OF DIABETES MELLITUS AND GLYCEMIC CONTROL

Hypoglycemic Drugs

The current approach to the treatment of type 2 diabetes mellitus depends on a combination of lifestyle modifications and oral agents (229). Although there is no reason why insulin should not be implemented early in the treatment of type 2 diabetes, the requirement for subcutaneous injection and the availability of new oral medications has relegated insulin therapy to a late intervention. Smoking cessation, weight loss, increased physical activity, and restricted calorie diets are the main lifestyle changes. The two most commonly used oral agents are the sulfonylureas, which stimulate insulin secretion, and metformin, which decreases hepatic glucose production and increases insulin sensitivity. Second generation sulfonylureas (glimepiride, gliclazide) may offer a survival advantage over older agents (glyburide), particularly when used in combination with metformin (230,231). Similar to sulfonylureas, glitinides (rapaglinide, nateglinide) also increase pancreatic insulin secretion. Two newer classes of hypoglycemics are the alphaglycosidase inhibitors, which inhibit gastrointestinal absorption of carbohydrates, and the thiazolidinediones (TZDs). TZDs, including rosiglitazone and pioglitazone, enhance insulin sensitivity and decrease insulin resistance by binding to PPAR-\(\gamma\), a nuclear receptor involved in adipose and vascular cell differentiation (232). TZDs also decrease inflammatory mediators (233), improve endothelial-dependent vascular responses (234), decrease thrombotic potential by decreasing plasminogen activator inhibitor levels (235), improve the diabetic atherogenic profile by increasing LDL particle size (236), reduce serum CRP levels (237), and reduce carotid intimal thickness (238).

In the recently reported PIOSTAT study, a prospective double-blind trial, 125 high-risk patients were randomized to pioglitazone or simvastatin plus placebo or to a combination of pioglitazone and simvastatin. At 12 weeks both pioglitazone and simvastatin significantly reduced high-sensitivity CRP and the combination regimen showed additive effect (239). Whether these pleiotropic actions of TZDs will translate into improved clinical outcomes in patients with diabetes remains under investigation. The PROspective PioglitAzone Clinical Trial In MacroVascular Events (PROactive) study (240) was a placebo-controlled trial of 5238 patients with type 2 diabetes and significant macrovascular disease at baseline who were randomized to pioglitazone or placebo. The study sought to achieve similar levels of glucose control in the two arms and attempted to reach specific hemoglobin A1c levels. The pioglitazone-treated patients had a nonsignificant 10% reduction in the primary composite endpoint of all-cause mortality, nonfatal MI, stroke, ACS, coronary or lower extremity revascularization, or amputation above the ankle \((p = 0.095)\). However, pioglitazone significantly reduced the secondary endpoint, a composite of all-cause mortality, nonfatal MI, and stroke \((RR 16\%; p = 0.027)\). A subsequent analysis of a subgroup of high-risk patients with prior MI (241) found that pioglitazone significantly reduced the incidence of fatal and nonfatal MI (absolute reduction 1.9\%; \(p = 0.045\)) and of ACS (absolute reduction 1.8\%; \(p = 0.035\)). However, the incidence of heart failure requiring hospitalization was 7.5\% in the pioglitazone group and 5.2\% in the placebo group.

In the A Diabetes Outcome Progression Trial (ADOPT) study, rosiglitazone monotherapy maintained long-term glycemic control in newly diagnosed type 2 diabetics
better than either metformin or glyburide monotherapy (242). However, glyburide was associated with a lower risk of cardiovascular events (mainly heart failure) than rosiglitazone \((p < 0.05)\) or metformin, while rosiglitazone was associated with more weight gain and edema than either metformin or glyburide.

A recent meta-analysis of 42 randomized controlled trials in which rosiglitazone was compared with either placebo or another hypoglycemic drug has raised additional serious concerns (243). In this analysis, rosiglitazone was associated with a significant increase in the risk of MI \((p = 0.03)\) and a trend toward an increase in the risk of death from cardiovascular causes \((p = 0.06)\). It should be noted that the absolute number of adverse effects was small, that the meta-analysis has several limitations and that, as of this writing, it has not undergone careful scrutiny. Nevertheless, despite recent enthusiasm for the use of TZDs as hypoglycemic agents, caution is advisable in prescribing these agents until more information is available and the complex actions of peroxisome proliferator-activated receptors (PPAR) agonists are better understood. Furthermore, it is now clear that TZDs should not be used to treat diabetic patients with heart failure or severe left ventricular dysfunction, since these agents have been shown to cause fluid retention and aggravate or precipitate heart failure even though they do not appear to adversely affect left ventricular systolic function (244).

The newest classes of hypoglycemic agents used to treat diabetes are the incretin mimetics (exenatide) and the incretin enhancers (sitagliptin). Incretin is a gut-derived hormone that stimulates insulin, suppresses glucagon secretion, inhibits gastric emptying, and reduces appetite and food intake. Clinical trials with exenatide have shown reductions in fasting and post-prandial blood glucose and HbA1c with an associated weight loss. Sitagliptin has been shown to reduce HbA1c by 0.5% to 1.0% with no associated weight gain (245). The effect of these new agents on the macrovascular complications and cardiovascular outcomes of patients with type 2 diabetes is yet to be determined.

**Glycemic Control**

The question of whether “tight” glycemic control reduces the risk of cardiovascular events is still under investigation. The Diabetes Control and Complication Trial (DCCT) demonstrated that tight glycemic control reduced the occurrence or progression of diabetic microvascular complications in type 1 diabetic patients (39). However, the effect of glycemic control on macrovascular complications is less clear. In the DCCT study, a trend toward less cardiovascular morbidity and mortality in type 1 diabetics was not statistically significant. In addition, the 18-month DCCT follow-up study (EDIC) of 1325 type 1 diabetic patients demonstrated that neither intensive therapy nor the glycosylated hemoglobin level affected carotid intimal thickness (246). Nonetheless, during long-term follow-up (mean 6.5 years) intensive glycemic control reduced the risk of any cardiovascular event by 42\% \((p = 0.02)\) and the risk of cardiovascular death, nonfatal MI, or stroke by 57\% \((p = 0.02)\) (247).

The UKPDS established that aggressive glycemic control reduces microvascular disease in type 2 diabetics. However, the effect of this intervention on macrovascular disease was modest, the reduction of macrovascular complications failed to reach significance, and cardiovascular outcomes did not differ between patients treated with sulfonylureas or insulin (40). Nonetheless, subsequent analysis of the UKPDS data (248) found that each 1\% decline in HbA1c was associated with a 21\% relative reduction in diabetes-related mortality, a 14\% reduction in MI, and a 37\% reduction in microvascular complications (all statistically significant). The Veterans Affairs Diabetes Feasibility
Trial (249) was a study of 350 men with a mean age of 60 years and an average duration of type 2 diabetes of 7.8 years who were randomized to either standard or intensive management. This study demonstrated no differences in total or cardiovascular mortality in the intensive versus standard treatment arms despite a 2% difference in glycated hemoglobin levels during the 27-month follow-up period.

The impact of tight glycemic control at the time of cardiac surgery and PCI has also been studied extensively and remains controversial with conflicting results reported. Intraoperative hyperglycemia has been shown to be an independent risk factor for complications, including death, after cardiac surgery (250). Similarly, hyperglycemia at the time of PCI may promote restenosis in diabetic patients (251). Some studies have reported improved CABG surgery outcomes in patients treated intraoperatively with GIK (252) or with continuous insulin infusion (253), whereas others have not. For example, in a recent single-center study of intensive intraoperative insulin therapy versus conventional glycemic management during cardiac surgery, perioperative morbidity and mortality did not differ in the two groups (254). Despite these conflicting reports, the preponderance of evidence suggests that maintenance of normoglycemia and treatment with insulin-based regimens is beneficial and reduces both morbidity and mortality (albeit modestly) in critically ill patients and in patients undergoing surgical procedures or PCI (255).

Although, tight glycemic control appears to have a modest effect on morbidity and mortality from cardiovascular disease in patients with diabetes mellitus, no studies have systematically evaluated the impact of intensive glucose control in diabetic patients older than 65 years. The multifactorial etiology of macrovascular disease suggests that optimal treatment of diabetic patients includes blood pressure management, correction of dyslipidemia, and modifying other prevalent risk factors (e.g., tobacco use, obesity, physical inactivity). The results of the recently reported Steno-2 study confirm that a multifactorial approach that includes intensive treatment of hyperglycemia, hypertension, dyslipidemia, microalbuminuria, and behavior modification in conjunction with aspirin reduces the risk of cardiovascular events in patients with type 2 diabetes by about 50% (256). Further large-scale, prospective, and randomized trials are necessary to determine the role of aggressive glycemic control in the prevention of diabetic macrovascular disease, particularly in older adults.

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Epidemiology of Coronary Heart Disease in the Elderly

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INTRODUCTION

Coronary heart disease (CHD) is the central component of a broad spectrum of disease conditions affecting the heart and circulation, collectively termed atherosclerotic cardiovascular disease, that progress dramatically as age advances. Although CHD in all its clinical manifestations contributes significantly to disability and death throughout life, its toll is heaviest in the elderly (1–7). Because there is a substantial paucity of epidemiological information regarding both the development and prevention of CHD in the elderly, a thorough evaluation of the role of risk factors for CHD in older persons and the potential benefits of their amelioration would represent an important contribution to the clinical and preventive management of this disease in a large segment of the United States and world population.

Considerations regarding the character of CHD and the role of risk factors for its development in older persons, which at the surface may appear straightforward, are in actuality quite complex because, of necessity, they involve interactions of the multiple and overlapping domains of aging, disease, and risk factors. This complexity is captured in the form of a Venn diagram proposed by Lakatta and his colleagues (8) (Fig. 1).

In this representation, aging denotes the constellation of processes occurring over time in the adult organism resulting in characteristic alterations of structure and function of body tissues and organs including the heart and blood vessels. CHD represents “disease” in this context with underlying anatomical and pathophysiological features ultimately manifested as clinical symptoms and complications. Risk factors, in turn, index an array of atherogenic personal traits as well as lifestyle characteristics, including diet and exercise, which are associated with the development of CHD (9).
Separate perspectives for each interaction among these three domains will, therefore, constitute the framework for further discussion. First, we will examine the relation of CHD occurrence to advancing age and the character of CHD in older persons. Next, we will examine how established risk factors for CHD change with advancing age and their prevalence in the elderly. Finally, we will examine associations between specific risk factors and CHD in the elderly and comment on available information regarding the efficacy of treating such factors.

Each of these perspectives is systematically examined in 30-year follow-up data from the Framingham Study, focusing on findings in subjects aged 65 to 94 years. Details of the examination and laboratory procedures, response rates, and criteria for disease outcomes in the Framingham Study have previously been described (10).

**CHD IN THE ELDERLY**

A fundamental observation of cardiovascular disease epidemiology is the distinct age-related rise in the incidence of nearly all manifestations of heart and circulatory disease across the lifespan. In addition to CHD, such cardiovascular disease conditions include stroke, peripheral arterial disease, and chronic heart failure. The increase in incidence of CHD with advancing age is clearly the most striking (Fig. 2) and illustrates the most important element of the first perspective (i.e., the relation between aging and CHD). Although calculated incidence rates in men and women at far-advanced age are based on relatively small numbers of CHD events, such rates clearly follow trends established earlier in life. Also, while incidence rates in men increase linearly with age, those in women tend to increase more steeply at advanced age, approximating an exponential function.

Similar trends of increasing incidence of disease events with age as noted in Figure 2 are observed in Framingham Study data for both men and women up to age 84 for nearly every major clinical manifestation of CHD, including angina pectoris, myocardial infarction, sudden death, and death due to CHD (10).
Another important observation regarding the relation of CHD and advancing age is the progressive attenuation of male predominance of disease. This is illustrated in Figure 3, which shows the marked decline in male-to-female ratio of incidence rates for CHD with the relation crossing the line of identity at far-advanced age.
The character of CHD according to specified clinical manifestations for older men and women in the Framingham cohort is presented in Table 1. Data indicate the proportion of total coronary events represented by a specific manifestation. Symptomatic categories are not mutually exclusive and percentages exceed 100% because a given subject may have more than one clinical manifestation at the time of their initial presentation within a biennial period. Myocardial infarction represents the most common initial manifestation for CHD in older men, whereas angina pectoris appears to be the most common presenting feature in older women. Angina pectoris in older women frequently occurs as an isolated clinical entity. Angina pectoris in older men, however, is more often associated with acute myocardial infarction, either preceding or occurring after the acute event. Coronary insufficiency is the traditional term for unstable angina pectoris, referring to the clinical situation of either prolonged chest pain or a progressive increase in the frequency and/or intensity of ischemic chest pain. This manifestation occurs at similar frequencies in older men and women. Sudden death, as an initial manifestation of CHD, occurs somewhat more frequently in older men than in older women.

Another characteristic of CHD in the elderly is the tendency for a larger proportion of myocardial infarction events to be clinically unrecognized (Table 2). The diagnosis of myocardial infarction in such instances is based on the occurrence of unequivocal electrocardiographic changes consistent with infarction between biennial examinations, where neither the subject nor his/her physician has suspected the diagnosis (11). Symptoms associated with such events are usually attributed to musculoskeletal chest discomfort, upper gastrointestinal tract upset, gall bladder disease, or other conditions. Approximately one-half of such infarctions are completely silent. Unrecognized events represent a larger proportion of all infarctions in women, and particularly older women.

### Table 1

<table>
<thead>
<tr>
<th>Manifestation</th>
<th>Men</th>
<th>Women</th>
</tr>
</thead>
<tbody>
<tr>
<td>Myocardial infarction</td>
<td>135/244 (55%)</td>
<td>108/269 (40%)</td>
</tr>
<tr>
<td>Angina pectoris</td>
<td>73/244 (30%)</td>
<td>123/269 (45%)</td>
</tr>
<tr>
<td>Coronary insufficiency</td>
<td>16/244 (07%)</td>
<td>21/269 (8%)</td>
</tr>
<tr>
<td>Sudden death</td>
<td>37/244 (15%)</td>
<td>31/269 (12%)</td>
</tr>
</tbody>
</table>

*Source: Framingham Study, 30-year follow-up.*

### Table 2

<table>
<thead>
<tr>
<th>Age (yr)</th>
<th>Men (%)</th>
<th>Women (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>30–44</td>
<td>29</td>
<td>—</td>
</tr>
<tr>
<td>45–54</td>
<td>18</td>
<td>41</td>
</tr>
<tr>
<td>55–64</td>
<td>25</td>
<td>31</td>
</tr>
<tr>
<td>65–74</td>
<td>25</td>
<td>35</td>
</tr>
<tr>
<td>75–84</td>
<td>42</td>
<td>36</td>
</tr>
<tr>
<td>85–95%</td>
<td>33</td>
<td>46</td>
</tr>
<tr>
<td>Average</td>
<td>28</td>
<td>35</td>
</tr>
</tbody>
</table>

*Source: Framingham Study, 30-year follow-up.*
CHANGES IN CHD RISK FACTORS WITH ADVANCING AGE

Nearly all of the established CHD risk factors change with advancing age. These include changes in blood pressure, serum lipids, cigarette smoking, glucose metabolism, body weight, and other factors. Several age-related trends in risk factors and their prevalence in older persons are described below. This constitutes the second perspective of our discussion (i.e., the interaction between aging and risk factors).

The most well-characterized change in an established CHD risk factor with age is elevation of blood pressure. In longitudinal data from the Framingham Study, systolic blood pressure is observed to rise nearly linearly with advancing age in both men and women (Fig. 4). Diastolic blood pressure, in contrast, tends to rise throughout middle age in both sexes and actually declines at advanced age. Diastolic blood pressures in women, however, usually remain 5 to 10 mmHg lower than those in men throughout the life span (1).

The consistent increase in systolic blood pressure is due to progressive vascular stiffening attributable to alterations of the physicochemical properties within the media of the arterial wall, including overall thickening and changes in the nature and content of collagen, elastin, and, possibly, other structural proteins that occur with advancing age (12). This process is dissimilar to that of atherosclerosis, which underlies the preponderance of cardiovascular disease observed in older people.

Although progressive elevation of systolic blood pressure with advancing age is consistently observed in nearly every western industrialized population studied, it does not appear to represent a universal feature of the aging process. Data from a number of isolated primitive populations suggests that this relation is markedly blunted (13).

Figure 4  Average age trends in systolic and diastolic blood pressure levels for men and women based on cross-sectional and longitudinal (cohort) data. Framingham Study, Biennial exams 3–10. Source: From Ref. 1.
Possibilities accounting for differences in age-related change in blood pressure between populations likely include genetic factors as well as dietary influences, especially the higher intake of salt in industrialized nations (14).

Despite its ubiquity, however, progressive elevation of systolic blood pressure with advancing age should not be construed as an innocuous concomitant of the aging process, since it clearly confers increased risk for stroke, CHD, and other cardiovascular disease events in both elderly men and women (15). Elevated diastolic blood pressure also occurs commonly in the elderly and remains an important risk factor for cardiovascular disease, particularly in older men.

As a consequence of the progressive, age-related increase, primarily in systolic blood pressure, approximately 40–50% of men and women in a typical westernized population such as Framingham meet one or more of the established criteria for hypertension after the age of 65. For persons categorized as being hypertensive, isolated systolic hypertension (defined as systolic blood pressure (BP) >160 mmHg with diastolic BP <95 mmHg) accounts for nearly two-thirds of the total prevalence of hypertension in both older men and women (16). Combined hypertension, characterized by abnormal elevations of both systolic and diastolic blood pressures, accounts for less than one-third of the total prevalence. Isolated diastolic hypertension is considerably less prevalent in older men and women accounting for less than 15% of the prevalence.

Blood lipids including serum total cholesterol also vary with age across the life span and trends appear to be different in women compared with men. Figure 5 shows longitudinal trends in average levels of serum cholesterol in the Framingham Study as a function of age. Note that levels in men tend to peak in early middle age and then slowly decline with advancing age. Levels in women peak later in middle age and remain relatively high until advanced age before a decline occurs. The practical implication of this trend is the relatively high prevalence of hypercholesterolemia likely to be encountered in similar populations of older women.

Corresponding age trends for specific lipoprotein–cholesterol subfractions in the Framingham Study are illustrated in Figure 6. Trends for low-density lipoprotein (LDL)
cholesterol, in general, are similar to those for serum total cholesterol. Mean levels of high-density lipoprotein (HDL) cholesterol are consistently higher in women than in men across the age span, but tend to decline slightly after menopause. Mean HDL cholesterol levels in men remain essentially unchanged throughout life. Mean values of very low-density lipoproteins (VLDL) tend to be higher in men than women, but levels in both men and women tend to rise throughout middle age and then remain relatively stable thereafter. Presumably, these trends reflect fluctuations in body weight occurring at corresponding ages in the sexes.

The prevalence of major cardiovascular risk factors in older subjects of the Framingham Study is presented in Table 3. Data are arrayed for each decade of age from 65 to 94 years and separately for men and women.

As would be expected from age trends observed earlier, hypercholesterolemia appears to be quite prevalent in older women. Glucose metabolism becomes progressively impaired with advancing age, resulting in increasing prevalence of glucose intolerance in both older men and women (17). Body weight tends to decrease at a far-advanced age. Weight loss, however, represents a reduction primarily in lean body mass (i.e., muscle and bone tissue) rather than adipose tissue. The result is an alteration of body composition in older persons with higher proportional adiposity per unit of weight (18). Despite the tendency for lower body weights at advanced age, obesity appears to be well represented in both older men and women in this cohort. The prevalence of cigarette smoking appears to decrease with advancing age. This can be attributed not only to higher mortality rates in smokers but also to discontinuation of cigarettes because of health problems or concerns in older persons. The prevalence of ECG left ventricular hypertrophy (LVH) increases with advancing age in both older men and women.

From the foregoing analysis, it is clear that the majority of established risk factors for CHD in middle-aged persons are prevalent in the elderly. What remains is the task of

Figure 6 Average age trends in lipoprotein cholesterol subfractions. Framingham Study.
marshaling evidence to address the question of whether or not such risk factors continue to remain operative in the development of CHD in older persons. This analysis constitutes the third and final perspective of interactions alluded to earlier (i.e., associations between specific risk factors and CHD in older persons), which will be reviewed next.

ASSOCIATION BETWEEN SPECIFIC RISK FACTORS AND CHD IN THE ELDERLY

Associations for a number of specific risk factors and CHD are summarized in Table 4. Putative risk factors are listed in the column on the left. Standardized, age-adjusted (bivariate) logistic regression coefficients are categorized for younger and older subjects.

Table 4  Associations Between Specific Risk Factors and Incidence of Coronary Heart Disease

<table>
<thead>
<tr>
<th>Risk factors</th>
<th>Ages 35–64</th>
<th></th>
<th>Ages 65–94</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Men</td>
<td>Women</td>
<td>Men</td>
<td>Women</td>
</tr>
<tr>
<td>Systolic pressure</td>
<td>0.338a</td>
<td>0.418a</td>
<td>0.401a</td>
<td>0.286a</td>
</tr>
<tr>
<td>Diastolic pressure</td>
<td>0.321a</td>
<td>0.363a</td>
<td>0.296a</td>
<td>0.082</td>
</tr>
<tr>
<td>Serum cholesterol</td>
<td>0.322a</td>
<td>0.307a</td>
<td>0.121</td>
<td>0.213a</td>
</tr>
<tr>
<td>Cigarettes</td>
<td>0.259a</td>
<td>0.095</td>
<td>-0.017</td>
<td>-0.034</td>
</tr>
<tr>
<td>Blood glucose</td>
<td>0.043</td>
<td>0.206a</td>
<td>0.1 66a</td>
<td>0.209a</td>
</tr>
<tr>
<td>Vital capacity</td>
<td>-0.1 12b</td>
<td>-0.331a</td>
<td>-0.127</td>
<td>-0.253b</td>
</tr>
<tr>
<td>Relative weight</td>
<td>0.190a</td>
<td>0.264a</td>
<td>0.177b</td>
<td>0.124b</td>
</tr>
</tbody>
</table>

*aSignificant at \( p < 0.001 \).
*bSignificant at \( p < 0.05 \).
*cSignificant at \( p < 0.01 \).

Source: Framingham Study, 30-year follow-up.
Epidemiology of Coronary Heart Disease in the Elderly

of the Framingham cohort and also arrayed separately for men and women. Regression coefficients are derived using a logistic regression model to mathematically relate the level of a risk factor or its categorical value to the development of CHD events. The magnitude of the coefficient and also the level of statistical significance reflect the strength of the association between the specific risk factor and CHD for the age group and sex under consideration.

A cursory inspection of the results indicates that the majority of significant associations between risk factors and CHD, apparent in younger men and women, remain significant in older age groups but not consistently in both sexes. Systolic blood pressure, for example, demonstrates strong risk associations for CHD in younger men and women and maintains strong associations in both older men and women. The risk association for diastolic blood pressure, in contrast, appears to lose significance in older women. Serum total cholesterol demonstrates strong risk associations for CHD in younger men and women; however, the strength of this risk association clearly weakens in older men but remains significant in older women. Cigarette smoking modeled using this methodology fails to show significant risk associations in either older men or women. Blood glucose levels, as well as other parameters reflecting impaired glucose metabolism including glucose intolerance and diabetes mellitus show strong risk associations for CHD in both older men and women. Vital capacity demonstrates strong negative risk associations, particularly in older women. Of interest, significant risk associations between CHD and body weight expressed as Metropolitan Relative Weight are maintained in both older men and women. A number of these risk associations will be characterized in detail below.

Similar data for associations between specific risk factors and CHD incidence can be derived using an alternative regression methodology, the Cox proportional hazards model (19).

Blood Pressure and Hypertension

The relation between blood pressure and CHD, particularly in older persons, represents one of the most striking risk associations in the Framingham Study. Risk relations between CHD incidence and systolic blood pressure in men and women are shown in Figure 7. CHD incidence, expressed as age-adjusted annual rate of CHD events per 1000, appears on the ordinates of left and right panels, respectively. Systolic blood pressure appears on the abscissas of both panels. Two risk relations are illustrated in each panel, one for younger men and women, aged 35 to 64, another for older men and women, aged 65 to 94. While overall incidence rates for CHD in women are substantially lower than those at corresponding blood pressures in men, the same underlying risk associations are observed. Note that CHD risk for systolic blood pressure rises with increasing pressure in all age groups and that this rise is even more striking in older than in younger persons. These trends are interpreted as marked increases in relative risk indicating that progressively higher levels of blood pressure confer additional risk for CHD. Although these trends do not establish causality, they serve to emphasize an important role for blood pressure in the extended sequence of pathophysiological events that result in manifest CHD. Also note that risk relations in older men and women are configured well above those of younger persons in each sex indicating substantially higher incidence rates for CHD at similar blood pressures. This is interpreted as an increase in absolute risk for CHD in older men and women, suggesting a substantially higher burden of disease at all levels of blood pressure in older compared with younger persons, even at normal or low blood pressures.
Risk relations between CHD incidence and systolic blood pressure in men and women are shown in Figure 7. Again, risk appears to rise with increasing blood pressure in all age groups (i.e., increased relative risk) and incidence rates at the same level of blood pressure are higher in older than in younger persons (i.e., increased absolute risk). Although there is a minor deviation from the nearly linear trend for the relation between systolic blood pressure and CHD incidence.

Risk relations between CHD incidence and diastolic blood pressure in men and women are shown in Figure 8. Again, risk appears to rise with increasing blood pressure in all age groups (i.e., increased relative risk) and incidence rates at the same level of blood pressure are higher in older than in younger persons (i.e., increased absolute risk). Although there is a minor deviation from the nearly linear trend for the relation between diastolic blood pressure and CHD incidence.
diastolic blood pressure and CHD incidence in older men, the relation maintains strong statistical significance. In contrast, the deviation in the relation corresponding to the fourth level of diastolic blood pressure (95–104 mmHg) in older women yields a statistically insignificant result using the logistic regression model, despite an apparent upward curvilinear trend. Although the discontinuities in these curves remain unexplained, these findings suggest a more consistent and reliable role for systolic compared with diastolic blood pressure as a predictor for CHD in both elderly men and women.

Risk gradients for CHD that, in general, are similar in direction and magnitude to those suggested earlier are observed when individuals are classified according to hypertensive status instead of absolute levels of blood pressure (Table 5). For all age and sex groups considered, the overall risk of CHD is two to three times higher in subjects with definite hypertension compared with normotensives, while risk is intermediate for those with mild hypertension. Absolute risk is two to three times higher in older subjects, both in men and women, and risk is nearly always higher in men than in women, regardless of age. Similar patterns of risk attributable to hypertension have been observed specifically for cerebrovascular events, heart failure, and peripheral vascular disease (15). When considered alone, isolated systolic hypertension also confers substantial risk for CHD and other cardiovascular disease outcomes.

Randomized clinical trials established the efficacy of treating combined elevations of systolic and diastolic blood pressures in older hypertensives (20,21), but uncertainty remained regarding the treatment of isolated systolic hypertension. The findings of the Systolic Hypertension in the Elderly Program (SHEP) served to dispel much of this uncertainty (22). This study documented impressive reductions in total numbers of fatal and nonfatal strokes in the active treatment group compared with the placebo group. Statistically significant reductions in nonfatal myocardial infarctions and coronary death, as well as combined CHD and total cardiovascular disease outcomes, were also noted in the group on active treatment. There appeared to be little or no evidence in this study that lowering of either systolic or diastolic blood pressure resulted in an increased risk of CHD events or mortality, particularly at the lower end of the distribution for blood pressure, the so-called J-shaped curve.

Six other clinical trials of drug therapy for hypertension in the elderly that included patients with isolated systolic hypertension also showed beneficial effects (23–28). In addition to substantial reductions in cerebrovascular events and heart failure, the majority of intervention studies of drug therapy for hypertension in older persons have consistently

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**Table 5**  Risk of CHD by Hypertensive Status According to Age and Sex

<table>
<thead>
<tr>
<th>Hypertensive status</th>
<th>Average annual age-adjusted rate per 1000</th>
<th>Coronary heart disease</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>35–64 yr</td>
</tr>
<tr>
<td></td>
<td></td>
<td>65–94 yr</td>
</tr>
<tr>
<td></td>
<td>Men</td>
<td>Women</td>
</tr>
<tr>
<td>Normal (&lt;140/90 mmHg)</td>
<td>8</td>
<td>3</td>
</tr>
<tr>
<td>Mild (140–160/90–95 mmHg)</td>
<td>15</td>
<td>7</td>
</tr>
<tr>
<td>Definite (&gt;160/95 mmHg)</td>
<td>21</td>
<td>10</td>
</tr>
</tbody>
</table>

*All trends significant at $p < 0.001$.

Source: Framingham Study, 30-year follow-up.
demonstrated either beneficial trends or significant reductions in CHD events and mortality. In contrast, drug therapy is less consistently associated with improved CHD outcomes in clinical trials involving predominantly middle-aged hypertensives (20,21,29).

The clinical evaluation and treatment of the elderly hypertensive patient are discussed in chapter 20.

Blood Lipids

The risk of CHD in older persons attributable to serum lipids represents an area of considerable uncertainty and controversy.

Relations between CHD incidence and serum total cholesterol in the Framingham Study are shown in Figure 9. Separate trends are plotted in younger and older subjects for men and women, respectively. Note that absolute risk is substantially increased in older compared with younger men. Note also that relative risk clearly rises over the entire distribution of serum total cholesterol in younger as well as older men. The break in continuity of the risk relation at the fourth level of the distribution in older men, however, yields results that narrowly miss statistical significance both in bivariate (age-adjusted) and multivariate estimates using the logistic regression model, whereas the association remains strongly predictive in younger men. Although incidence rates for CHD at corresponding levels of cholesterol are lower in women than those in men, the same overall pattern pertains (i.e., an increase in both absolute and relative risk). In this instance, however, statistical significance is maintained in both younger and older women.

The finding that serum total cholesterol loses strength as a risk factor for CHD, particularly in older men of the Framingham cohort, has resulted in serious misinterpretation by some authors who have used this information to argue that serum lipids are not important risk factors for CHD in the elderly and that neither detection nor treatment is justified (30,31). However, this view is not warranted, since several other studies have clearly validated the role of serum total cholesterol as a predictor of CHD events in older men (32–38) and also older women (32,34,38).

**Figure 9** Risk of CHD by level of serum cholesterol according to specified age groups in men and women. Framingham Study, 30-year follow-up. **Abbreviation:** CHD, coronary heart disease.
Despite these findings, however, a meta-analysis encompassing data from 22 U.S. and international cohort studies concluded that serum cholesterol did indeed lose strength as a risk predictor for CHD mortality in older men and also in older women (39), a finding consistent with original observations made in data from the Framingham Study. Cholesterol emerges as a significant predictor of CHD death when steps are taken to adjust for factors related to frailty or other comorbid conditions that serve to confound this risk association (40,41).

Focusing on serum cholesterol as the sole measure of risk for CHD attributable to serum, lipids should now be considered obsolete based on our current understanding of lipoprotein subfractions and the availability of standardized laboratory methods to measure them in clinical practice. Substitution of either LDL or HDL cholesterol in the regression model fully restores statistical predictability for the risk relation between serum lipids and CHD (42). HDL cholesterol, in particular, has emerged as an important lipid moiety that adds substantial precision to assessing coronary risk at limited additional cost (43). Construction of a serum cholesterol/HDL ratio provides a highly accurate characterization of CHD risk in older men and women in the Framingham Study, which is illustrated in Figure 10. Indeed, data from Framingham as well as other studies confirm the overall reliability of the cholesterol/HDL ratio in assessing CHD risk in younger and older persons and in men as well as women (34,42,44,45). The rationale for this approach is that the ratio reliably captures the effect of a dynamic equilibrium of lipid transport into and out of body tissues, possibly including the intima of blood vessels.

Several studies have suggested that serum triglycerides may be important predictors for CHD in either older men or older women, but not consistently in both sexes (34,42,44,46). Despite these observations, the present consensus holds that elevated levels of serum triglycerides represent a risk marker for obesity, glucose intolerance, and low HDL levels, all of which confers risk for CHD and, to the extent possible, deserve preventive attention.

Data from intervention studies using dietary measures or drug therapy demonstrate the benefit of lipid alteration in reducing risk of CHD events, particularly in middle-aged

**Figure 10** Risk of CHD by total/HDL cholesterol ratios among men and women aged 50 to 90 years. Framingham Study, 26-year follow-up. **Abbreviations:** CHD, coronary heart disease; HDL, high-density lipoprotein.
men (47, 48). However, despite the high prevalence of lipid abnormalities in older adults, limited data are available from clinical trials regarding the safety and efficacy of treating these abnormalities, especially in the very elderly. Therefore, widespread application of drug therapy to reduce risk of CHD in older persons as an element of primary prevention is not warranted at the present time. Of considerable interest, information from five large clinical trials makes a compelling case for reducing elevated or even average levels of LDL cholesterol with drugs in patients with established CHD: angina pectoris or following myocardial infarction (48–54). Drug therapy for the secondary prevention of CHD events (i.e., in persons with preexisting CHD) appears to be beneficial in both middle-aged and older patients of both sexes. Most recent clinical trials have also demonstrated that statin therapy reduces the incidence of stroke events (55).

Current management of hypercholesterolemia for an older person considered to be at risk should consist of a highly individualized approach beginning with appropriate dietary measures and weight control before initiating a trial of specific drug therapy, preferably at lower doses, to achieve a carefully monitored lipid-lowering effect (56).

**Cigarette Smoking**

Cigarette smoking fails to demonstrate strong risk associations for total CHD events in either older men or older women using the logistic regression methodology indicated in Table 4. Significant risk associations, however, are discerned between cigarette smoking and death due to CHD (10). One explanation for this phenomenon is that smoking may be more closely related to lethal events than to outcomes composed of combinations of morbid and lethal events (55). Another explanation is that the cross-sectional pooling approach used in the analysis may classify long-term smokers who have discontinued cigarettes for relatively brief periods as nonsmokers, in effect diluting the strength of the association between the risk factor and the outcome (56). Because of these difficulties, the most reliable approach to assessing risk associations between cigarette smoking and cardiovascular morbidity or mortality is to model these events prospectively for defined categories of smoking behaviors (e.g., current smoker, former smoker, and never smoker) and for longer time intervals. Such approaches yield strong risk associations between cigarette smoking and a broad array of cardiovascular outcomes, including CHD, stroke, and peripheral arterial disease, even in older men and women. These observations have been documented using data from Framingham as well as other studies (33, 57–61).

Reducing the risk of cardiovascular disease is not the only reason to encourage discontinuation of cigarettes in older persons. Cigarettes contribute to the development of chronic bronchitis and obstructive lung disease as well as lung cancer and other malignancies. These conditions also exact a heavy toll in terms of disability and death in the elderly. Thus, the clinician can make a compelling argument that it is never too late to stop smoking and extend appropriate advice and encouragement to assist patients in their effort to discontinue cigarettes.

**Glucose Tolerance and Diabetes Mellitus**

Impaired glucose metabolism is not only highly prevalent in the elderly, but also confers substantial risk for CHD as well as other cardiovascular events in both older men and women. Various measures of glucose tolerance are employed and nearly all demonstrate significant risk associations with CHD in the Framingham Study (10). These measures include blood glucose levels, glycosuria, and the composite risk categories designated as glucose intolerance and diabetes mellitus. Although diabetes mellitus confers enhanced
risk for both younger and older men, the impact of diabetes mellitus on CHD risk is even greater for both younger and older women (62) (Fig. 11). Similar patterns of risk are noted for coronary and cardiovascular mortality (10,62,63). Diabetes also emerges as an important risk factor in the development of chronic heart failure, particularly in older women with insulin-dependent diabetes mellitus (64). Presumably, the microvascular disease that is unique to diabetes, as well as other mechanisms, serves to produce progressive damage to heart muscle, ultimately resulting in compromised ventricular function and heart failure.

There is little evidence that control of hyperglycemia, either by oral hypoglycemic agents or insulin, effectively forestalls either the development or complications of cardiovascular disease (62,65), although encouraging trends in this regard were identified in the Diabetes Control and Complications Trial (66). Available evidence would, therefore, suggest that there is more to be gained in reducing risk by correcting associated cardiovascular risk factors in persons with diabetes than by attention confined to early detection and control of hyperglycemia (67).

**Left Ventricular Hypertrophy**

LVH as determined by the electrocardiogram (ECG-LVH emerges as a strong risk factor for CHD in older men and women (Fig. 12). Marked increases in CHD incidence are noted in persons with voltage criteria for LVH alone, and additional risk is conferred by
definite LVH, which includes repolarization (ST and T wave) abnormalities consistent with LVH in addition to voltage criteria. These electrocardiographic findings presumably reflect abnormalities of myocardial structure and function related to early compromise of the underlying coronary circulation that antedate the development of clinical manifestations of CHD (68–70).

In this context, LVH (LV mass), as determined by echocardiography, has emerged as an extremely potent independent predictor of CHD as well as other cardiovascular disease events, especially in older persons (71,72).

**Body Weight**

Of considerable interest is the finding that increased body weight represents a significant risk marker for CHD even at advanced age. The association between body weight and risk for CHD in older subjects of the Framingham Study is illustrated in Figure 13. Note that while CHD risk rises more strikingly with increasing body weight in older men, trends in older women clearly indicate enhanced risk at higher body weights. These data are consistent with reports from other studies (73,74). Progressive increases in body weight occurring earlier in life correlate closely with changes in the levels of several risk factors considered to be more directly related to the pathogenesis of atherosclerosis (75). These include increases in blood pressure, serum cholesterol and triglycerides, blood glucose, and a reduction in HDL cholesterol. These findings emphasize the need to incorporate measures ultimately designed to either control or, if necessary, gradually reduce body weight as part of risk management even in older persons. Although a beneficial effect of weight reduction on CHD events in older adults has not been established, weight control should be incorporated into the initial management of elderly patients with hypertension, dyslipidemia, and diabetes, or combinations of these conditions.
Vital Capacity

Vital capacity is a simple and sensitive clinical technique for assessing compromise of pulmonary or cardiac function, or both, in individuals of all ages. In contrast to inconsistent risk associations with CHD found in younger subjects, vital capacity emerges as an important risk factor in the elderly, particularly with respect to risk for major coronary events (2,10). Vital capacity normally declines with advancing age, an effect that is strongly exacerbated by cigarette smoking and obesity (76). Diminished vital capacity in older people is also correlated with loss of muscular strength as assessed by handgrip, presumably reflecting overall neuromuscular debility (77). Low vital capacity is also a strong predictor of cardiovascular mortality, as well as mortality from all causes. Measurement of this parameter, therefore, should be considered as part of the standard risk assessment of all older patients.

Heart Rate

Recent data from the Framingham Study demonstrate that higher resting heart rate confers additional risk for CHD in both younger and older men, although no association is observed in younger or older women (2,10). An explanation for this finding is not readily apparent. Heart rate may be a more sensitive indicator of underlying cardiac dysfunction in men than in women, or the net impact of sympathetic nervous system influences in precipitating CHD events may be greater in men. High heart rates may also reflect physical deconditioning.

Physical Activity

Accumulating evidence suggests that lifetime vigorous physical activity may forestall CHD in the elderly (78–80). Previously reported data from Framingham indicated that
overall mortality including coronary mortality was inversely related to level of physical activity in middle-aged men (81), and a benefit in older men was also suggested. Although regular physical activity in the elderly is desirable and should be strongly encouraged, it would be unwise to place undue emphasis on this approach alone for reducing the risk for CHD.

Prevalent CHD

An important predictor of CHD events at all ages is the presence of antecedent CHD. It is, therefore, of interest that several of the risk factors associated with the initial development of CHD in the elderly not only continue to have strong correlations with prevalent disease but also maintain predictive associations for new CHD events in older persons with preexisting disease (34,36,82–84). Serum lipids, cigarette smoking, and diabetes appear to be more prominent in this context than hypertension. Blood pressure may fall substantially following myocardial infarction, especially extensive anterior myocardial infarction that carries a poorer prognosis, thereby confounding the relation between hypertension and CHD morbidity and mortality (85). Blood pressure, however, reemerges as a significant predictor of recurrent CHD events in long-term survivors of myocardial infarction (86).

These findings serve to emphasize the critical role of controlling risk factors in older persons with established CHD. Effective treatment of hypertension, discontinuation of cigarettes, and adequate control of hyperglycemia are important preventive measures in the clinical management of such individuals. Similarly, the potential benefit of lipid-lowering drugs in older persons with established CHD has been previously noted.

Other Risk Factors

Several hematological or hemostatic factors have been described as risk variables in the Framingham Study. Hematocrit appears to contribute to CHD in younger men and women but not in older persons (10). White blood cell count, which was strongly correlated with the number of cigarettes smoked per day, hematocrit, and vital capacity, was associated with enhanced risk for CHD and other cardiovascular endpoints in older men, both in smokers and nonsmokers, but only in women who smoked (87). These data are consistent with reports from other studies (88). Advanced age is associated with significant increases in plasma fibrinogen and von Willebrand factor levels as well as measures reflecting impaired fibrinolytic function: plasminogen-activator inhibitor (PAI) and tissue plasminogen-activator antigens (PAAs), contributing to a prothrombotic state in the elderly (89). In the Framingham Study, plasma fibrinogen showed strong risk associations for CHD and other cardiovascular disease outcomes in men, including older men (90), similar to findings from other studies (91). Significant risk associations, however, were not apparent in older women. Considerably less information is currently available regarding the cardiac risk potentially attributable to PAI and PAAs in older persons.

Elevated blood levels of homocysteine appear to be an independent risk factor for cardiovascular disease, particularly stroke in older persons, a finding confirmed in Framingham and other studies (92). Homocysteine has multiple deleterious effects on vascular endothelium ultimately leading to thrombosis (93). Factors that may increase homocysteine levels include advancing age, renal insufficiency, vitamin-deficient diets, and drugs that interact with folic acid and vitamins B₆ and B₁₂. Combinations of folic acid and vitamins B₆ and B₁₂ are usually employed for therapy. Data from several recent large controlled clinical trials, however, have failed to demonstrate a significant benefit of
lowering homocysteine on subsequent atherothrombotic events (94–96). This has served to limit the enthusiasm of many clinicians to screen for and treat hyperhomocysteinemia in patients with established CHD. Because of the relative safety and inexpensive nature of such therapy, some clinicians prefer to maintain high-risk patients on these vitamin preparations. The possibility that reducing homocysteine levels may have a role in the primary prevention of CHD has yet to be confirmed.

Inflammatory phenomena are now recognized as playing a central role in the extended pathophysiological processes resulting in atherosclerosis and its thrombotic complications. Levels of high-sensitivity C-reactive protein (CRP), a marker of systemic inflammation, represent a strong predictor of both initial and recurrent CHD events (97,98). Because drugs such as aspirin and statins can attenuate this inflammatory process, CRP may have an important role in identification of apparently healthy older individuals, particularly women, at enhanced risk for CHD who may benefit from primary prevention (99). CRP levels can also serve as a clinically useful guide for an array of cardioprotective therapies already validated in the secondary prevention of CHD events in patients with established CHD, irrespective of age.

A key study in this context evaluated the utility of combining CRP with other inflammatory markers including soluble tumor necrosis factor (TNFα) receptor types 1 and 2 (sTNF-R1 and sTNF-R2) and interleukin 6 (IL6) in middle-aged and older men and women (100). High levels of IL6 and CRP were significantly related to risk of CHD in both sexes, whereas high levels of soluble TNFα were significant only in women. Although all associations were attenuated following statistical adjustment for lipid and nonlipid factors, CRP alone retained power as an independent predictor for CHD.

Myeloperoxidase (MPO) is a hemiperoxidase secreted by both white blood cells and activated phagocytes at sites of inflammation including atherosclerotic lesions. Accumulating evidence suggests that MPO may play a causal role in plaque vulnerability leading to subsequent rupture (98). A recent prospective study demonstrated that serum MPO levels are associated with future risk of CHD events in apparently healthy middle-aged and older persons (101).

Assays of natriuretic peptides have already established their utility in the evaluation and management of patients with heart failure. Both brain plasma natriuretic peptide and N-terminal atrial natriuretic peptide levels are elevated in the elderly, especially in older women (102), but neither peptide level was associated with the subsequent risk of CHD events (103). Both peptide levels, however, were associated with significant risk for stroke, atrial fibrillation, heart failure and related death. Excess risk was apparent at natriuretic peptide levels well below those consistent with heart failure. Similar findings were reported in the recently completed Prevention of Events with Angiotensin-Converting Enzyme Inhibition (PEACE) Trial (104).

In a recent investigation from the Framingham Heart Study, an array of biomarkers was used to predict the risk of major cardiovascular events and death (105). These included CRP, both natriuretic peptides, aldosterone, renin, fibrinogen, D-dimer, PAI type 1, homocysteine, and urinary albumin-to-creatinine ratio. The biomarkers that most strongly predicted major cardiovascular events were B-type natriuretic peptide and urinary albumin-to-creatinine ratio. The authors concluded that the use of 10 contemporary biomarkers adds only moderately to traditional cardiac risk factors in assessing risk for CHD.

The potential utility of circulating vascular cell adhesion molecules (VCAMs) as risk markers for CHD at advanced age has received limited attention. Both VCAM-1 and intercellular adhesion molecule-1 (ICAM-1) appear to be elevated in older men and women irrespective of coronary risk status or established CHD (106). E-selectin was not
correlated with age. Such molecules appear to have limited value as risk predictors for CHD in the elderly at the present time.

An extensive array of psychosocial, occupational, dietary, and other factors have been described as putative risk parameters for CHD in the Framingham Study (9,107); however, only limited information is available regarding specific associations of these factors with CHD in older persons. Family history of CHD is strongly related to early development of CHD (before age 60) in both men and women in the Framingham Study, and predictive associations also remain significant for the late onset of CHD (108).

**CHD RISK PROFILES IN THE ELDERLY**

Although associations between a specific risk factor and CHD can be considered in isolation as a single relation, in many instances combinations of several risk factors may contribute to the observed risk profile, especially in older persons. Risk of CHD, in such instances, can be reliably estimated by synthesizing several risk factors into a composite score, based on a multiple logistic function (109–111). Risk factors are assessed by standard clinical procedures (smoking history, blood pressure, and electrocardiogram) and by routine laboratory studies (serum total cholesterol, HDL cholesterol, and blood glucose). This type of composite index permits detection of individuals at relatively high risk, either on the basis of marked elevation of a single factor or because of marginal abnormalities of several risk factors.

This multivariate risk scenario is illustrated in Figure 14, which characterizes the risk of CHD at two predefined levels of serum cholesterol and then considers changes in the levels or values of other risk factors toward worsening risk, as indicated in the accompanying table. Note that risk increases progressively with the addition of other risk factors for both categories of serum cholesterol, even in instances where a factor such as cigarette smoking has a relatively weak risk association with CHD when considered alone.

The major risk factors including age when taken together, explain only a limited proportion of the variance of CHD incidence in younger as well as older persons (109–111). It is likely that other major risk attributes exist among both the young and the elderly, but are yet to be identified. It must be emphasized, however, that the factors that

![Figure 14](https://example.com/image.png)

**Figure 14** Risk of CHD of two levels of serum cholesterol according to specified levels or categories of other risk factors for 70-year-old women in the Framingham Study. *Abbreviation:* CHD, coronary heart disease.
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have already been delineated do identify high-risk subgroups of the elderly population that should be targeted for preventive management (112,113).

PERSPECTIVES FOR PRIMARY PREVENTION OF CHD IN THE ELDERLY

An important principle of prevention is the concept that measures limiting the effect of known risk factors should be initiated as early in life as possible to minimize the subsequent development of disease in both the young and the elderly. It is inappropriate to conclude, however, that modifications of risk factors initiated at advanced age are unlikely to be effective in reducing the toll of related disease in older persons. A simple but important observation in this context is that the incidence of CHD in the elderly varies widely within distributions of continuous risk factors such as blood pressure or serum cholesterol. Incidence also appears to differ markedly for values of categorical variables such as the presence or absence of LVH. In addition, data presented earlier indicate that the incidence of CHD, as well as other cardiovascular disease events, is not only substantially higher in populations of older persons but also continues to rise with advancing age across the life span. Because incidence is usually higher in older persons, the beneficial effect of a given intervention such as treatment of hypertension or hypercholesterolemia, as assessed by reduction in relative risk, may be similar to or lower than that observed in younger persons (2,20,114). In many such instances, however, the impact measured as a difference in absolute risk, reflecting reduction in the number of adverse disease outcomes, is actually greater in the elderly. A corollary of this is that a smaller number of older compared with younger people need to be treated to prevent an equivalent number of disease events.

These considerations are more relevant today than ever before. Recently, a marked and progressive decline in mortality due to coronary and cardiovascular disease has occurred in the United States and several other industrialized nations (115). Age-specific trends indicate decreasing mortality due to CHD and cardiovascular disease, both in the elderly and in younger adults of both sexes. Similar trends in cardiovascular mortality have been identified in the Framingham population (116). At the same time, the prevalence of several coronary risk factors such as untreated hypertension, elevated serum cholesterol levels, and cigarette smoking has diminished in the population at large including the elderly, while major advances have occurred in the diagnosis and treatment of CHD. Importantly, in a recent analysis approximately 50% of the decline in cardiovascular mortality was attributed to the success of widespread implementation of primary preventive strategies resulting in lower levels of major risk factors, while the remaining 50% was attributed to advances in diagnosis and treatment of established disease (115).

In this context, hypertension clearly emerges as the dominant, potentially remediable risk factor for both CHD and cerebrovascular disease morbidity and mortality in the elderly. Hypertension is highly prevalent in the aged, easily detected, and can be corrected by the careful application of appropriate measures including drug therapy. As mentioned earlier, direct evidence from clinical trials has already established the efficacy of antihypertensive measures in reducing the frequency of both stroke and CHD events in elderly hypertensives. Available information also makes a compelling case for discontinuation of cigarettes at all ages including the elderly. Information is needed, however, regarding the feasibility and effectiveness of nonpharmacological approaches such as diet and weight reduction in treating older persons with hypertension and lipid
abnormalities, both as initial therapy and as adjuncts to specific drug therapy. Also, it is critically important that the efficacy and safety of drug therapy for the treatment of lipid abnormalities in the elderly for the purpose of primary prevention be established in large, well-designed clinical trials. Lack of such information severely limits our confidence in extending what may be a potentially highly beneficial preventive measure to greater numbers of older persons.

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INTRODUCTION

Coronary atherosclerosis is very common in the elderly population, with autopsy studies demonstrating a prevalence of at least 70% in persons over age 70 (1,2). These autopsy findings may be coincidental, with the disease clinically silent throughout the person’s life; however, only 15–30% of persons over age 65 show clinical manifestations of coronary heart disease (CHD). In the National Health and Nutrition Examination Survey (NHANES) 1999–2002, the prevalence of clinical CHD rose progressively with age, reaching 18.6% in men and 16.1% in women aged 75 years and above (3). Clinical CHD was present in 502 of 1160 men (43%) of mean age 80 years, and in 1019 of 2464 women (41%), of mean age 81 years in a long-term care facility (4). The marked discrepancy between the clinical and autopsy prevalence of CHD in the elderly indicates that CHD is often silent in this age group. Studies employing exercise testing and myocardial perfusion imaging in asymptomatic volunteers have demonstrated a striking age-related increase in silent myocardial ischemia, helping to reconcile differences in CHD prevalence between clinical and autopsy studies (5).

Unfortunately, even though CHD is so prevalent in elderly persons, the disease is often undiagnosed or misdiagnosed in this age group. Failure to correctly diagnose the disease in the elderly may be due to a difference in clinical manifestations in this age group compared with that of younger patients. Such differences may reflect a difference in the disease process between older and younger patients, or it may be related to the superimposition of normal aging changes on those of concomitant diseases that may mask the usual clinical manifestations.
Prevalence and extent of CHD increase with age. In the Coronary Artery Surgery Study, the prevalence of three-vessel CHD was 61% in patients aged 65 years and older versus 46% in those younger than 65 years; left main coronary artery stenosis was seen in 13% versus 9%, respectively (6). In a database of 21,573 patients undergoing cardiac catheterization between 1995 and 1998, left main coronary artery disease (CAD) increased in prevalence from 6.3% below age 70 to 13.9% in those 80 years and older (7). Multiple studies of patients undergoing percutaneous coronary interventions have also found higher prevalence of multivessel and left main disease in the elderly.

Coronary artery calcium is also more common in the elderly than in younger populations. In the community-based Rotterdam Study, 1795 volunteers (mean age 71 years) with no history of CHD underwent electron beam computed tomography to detect coronary artery calcium (8). Calcium scores greater than 100 were observed in 49% and scores greater than 400 in 25%, both markedly higher than in younger populations. In this study, scores of 401 to 1000 were associated with a fourfold risk of hard CHD events compared with those with scores less than or equal to 100 even after adjustment for standard CHD risk factors; scores greater than 1000 increased CHD risk more than eightfold (Fig. 1) (8). Thus, coronary artery calcium is highly prevalent in older volunteers free of clinical CHD and has similar adverse prognostic significance as in younger populations.

**MYOCARDIAL ISCHEMIA**

Exertional angina pectoris caused by myocardial ischemia is commonly the first manifestation of CHD in young and middle-aged persons. It is usually easily recognized because of its typical features; however, in the elderly, this may not be the case. Because
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of limited physical activity, many elderly persons with CHD will not experience exertional angina pectoris. Even when angina pectoris does occur, the patient and physician may often attribute it to a cause other than CHD. For example, myocardial ischemia, appearing as shoulder or back pain, may be misdiagnosed as degenerative joint disease or, if the pain is located in the epigastric area, it may be ascribed to peptic ulcer disease. Nocturnal or postprandial epigastric discomfort of a burning quality is often attributed to hiatus hernia or esophageal reflux instead of CHD. Postprandial angina pectoris tends to occur among elderly and hypertensive patients with severe CHD and a markedly reduced ischemic threshold (9). Furthermore, the presence of comorbid conditions, so frequent in the elderly patient, adds to the confusion and may lead to misdiagnosis of the patient's symptoms, which are actually due to myocardial ischemia.

Instead of typical angina pectoris, myocardial ischemia in elderly patients is commonly manifested as dyspnea, which is referred to as an "angina equivalent." Usually the dyspnea is exertional and is thought to be related to a transient rise in left ventricular (LV) end-diastolic pressure caused by ischemia superimposed on reduced ventricular compliance. Reduction in LV compliance may reflect normal aging changes or, more likely, is caused by the presence of coexisting hypertension and LV hypertrophy, disorders commonly present in elderly patients. Not infrequently, the dyspnea will occur in combination with angina pectoris, although the angina may be mild and of little concern to the patient.

In other elderly individuals, myocardial ischemia is manifested clinically as frank heart failure, with some patients presenting with acute pulmonary edema. Chest pain may not be present, although the myocardial ischemia is severe enough to produce a combination of diastolic and systolic LV dysfunction. Siegel and associates (10) reported on a group of elderly patients, mean age 69 years, with CHD in whom the disease manifested as acute pulmonary edema. The majority of patients were without angina pectoris, and many were without a prior history of CHD. Ninety percent, however, had a past history of hypertension, and their electrocardiogram (ECG) showed LV hypertrophy. Angiographically, the majority of patients had three-vessel CHD, although LV systolic function was only moderately depressed, with a mean LV ejection fraction of 43%. Over 60% of these patients underwent coronary bypass surgery or percutaneous transluminal angioplasty, and the long-term prognosis was excellent.

Similar findings have been reported in other studies of acute pulmonary edema caused by CHD (11–15). Graham and Vetrovec (15) compared patients with CHD hospitalized with acute pulmonary edema with patients hospitalized with angina pectoris without heart failure. The patients with acute pulmonary edema were older and, as in Siegel's study (10), most of the patients had preexisting hypertension. Three-vessel CHD was common in both groups, although angina pectoris was infrequent in patients with pulmonary edema. LV ejection fraction was more depressed in patients with pulmonary edema (42%) than in the angina pectoris group (59%). In another study, Kunis and associates (13) reported findings of a small group of elderly patients with CHD who had recurrent pulmonary edema that could not be prevented with medical therapy. Angiographic studies demonstrated three-vessel coronary disease with preserved LV systolic function. Only after undergoing coronary bypass surgery was the recurrent pulmonary edema prevented in these very elderly patients (13).

Another subset of elderly patients with CHD who present with acute pulmonary edema will demonstrating mitral valvular regurgitation that may be secondary to papillary muscle ischemia. In a study of 40 patients with acute pulmonary edema who had CHD, Stone and associates (16) found that 67% of the patients demonstrated moderate to severe mitral regurgitation on Doppler echocardiographic examination. The mean age of the
patients was 76 years. In the majority of patients (74%), a murmur of mitral regurgitation was not detected despite examination by multiple observers. The authors concluded that mitral valve regurgitation is not uncommon in elderly patients with CHD who present with acute LV failure and may contribute to the genesis of pulmonary edema.

In addition to having more severe CHD than younger patients, the elderly who undergo coronary arteriography demonstrate greater clinical instability, CHD complications, and comorbidities. In 21,573 patients, unstable angina pectoris was the indication for arteriography in 38% of persons aged 80 years and above versus 28% in those younger than 70 years (7). A history of heart failure was present, respectively, in 31% versus 11% of patients. Furthermore, comorbidities such as cerebrovascular and peripheral vascular disease, and chronic obstructive lung disease were two to three times more common in the elderly (7).

A single-center study by Tresch and associates (17) in a group of elderly patients (mean age 71 years) who underwent coronary arteriography showed similar findings. The initial manifestation in the majority of patients was unstable ischemic chest pain; 34% of the patients presented with an acute myocardial infarction. In 8% of these elderly patients, the initial manifestation was acute heart failure unassociated with an acute myocardial infarction. On cardiac catheterization, multivessel disease was common, although LV systolic function was often normal. Only 9% of the patient had an LV ejection fraction of less than 35%. In contrast, patients younger than 65 years more commonly sustained an acute myocardial infarction as the initial manifestation of CHD, were less likely to present with heart failure, and had less multivessel CHD (17).

Cardiac arrhythmias, particularly complex ventricular arrhythmias, may be a manifestation of myocardial ischemia in elderly patients with CHD. In Tresch’s study (17), 14% of elderly patients had arrhythmias as the initial manifestation of CHD. Sudden death may be the initial manifestation of CHD in older adults; in Framingham volunteers, 65 to 94 years old, CHD was manifest as sudden death in 15% of men and 12% of women (18).

Silent or asymptomatic myocardial ischemia is a common problem in elderly patients with CHD. Approximately 15% of the elderly patients in Tresch’s study (17) were asymptomatic, with myocardial ischemia detected by exercise stress testing during a preoperative evaluation. In a study of 185 nursing home patients with CHD, mean age 83 years, silent myocardial ischemia (SI) was detected by 24-hour ambulatory electrocardiography (AECG) in 34% (19). SI was detected by 24-hour AECG in 51 of 117 (44%) similar patients with CHD or hypertension and an abnormal LV ejection fraction (20). Hedblad et al. (21) detected SI by 24-hour AECG in 19 of 39 patients (49%) with CHD.

The reason for the frequent absence of chest pain in elderly patients with CAD is unclear. Various speculations have included (1) mental deterioration with inability to verbalize a sensation of pain, (2) better myocardial collateral circulation related to gradual progressive coronary artery narrowing, and (3) a decreased sensitivity to pain because of aging changes. Ambepitiya and associates (22) recently investigated the issue of age-associated changes in pain perception by comparing the time delay between the onset of 1 mm of electrocardiographic ST-segment depression and the onset of angina pectoris during exercise stress testing. The mean delay was 49 seconds in patients aged 70 to 82 years compared with 30 seconds in patients aged 42 to 59 years. The reason for this delay in perception of myocardial ischemia in the elderly is unexplained. The authors postulated that the impairment is most likely multifactorial in origin, involving peripheral mechanisms such as changes in the myocardial autonomic nerve endings with blunting of the perception of ischemic pain, as well as changes in central mechanisms. Another theory has suggested that the increase in SI and infarction in elderly patients with CHD is related to increased levels of, or receptor sensitivity to,
endogenous opioids (23). This explanation does not appear likely because studies have demonstrated a similar increase in response of β-endorphin levels to exercise in both elderly and younger patients (24), and animal studies show a decrease in opioid receptor responsivity with advancing age (25).

MYOCARDIAL INFARCTION

As with myocardial ischemia, some patients with myocardial infarction may be completely asymptomatic or the symptoms may be so vague that they are unrecognized by the patient or physician as an acute myocardial infarction. The Framingham Heart Study (26) found that, in the general population, approximately 25% of myocardial infarctions diagnosed by pathological Q-waves on ECG were clinically unrecognized and, of these, 48% were truly silent. The incidence increased with age, with 42% of infarctions clinically silent in men aged 75 to 84 years. In women, the proportion of unrecognized myocardial infarctions was greater than in men, but the incidence was unaffected by increasing age. Other studies (27–34) have also reported a high prevalence of silent or unrecognized myocardial infarction in elderly patients, with rates from 21% to 68% (Table 1). These studies also demonstrated that the incidence of new coronary events, including recurrent myocardial infarction, ventricular fibrillation, and sudden death, in patients with unrecognized myocardial infarction is similar to (26,31–33,35) or higher (34) than in patients with recognized myocardial infarction.

Symptoms when present in elderly patients with an acute myocardial infarction may be extremely vague and, as with myocardial ischemia, the diagnosis may be easily missed. Numerous studies have demonstrated the atypical features and wide variability of symptoms in elderly patients with acute myocardial infarction (Table 2) (27–29,36–40). Rodstein (27) found that in 52 elderly patients with acute myocardial infarction, 31% had no symptoms, 29% had chest pain, and 38% had dyspnea, neurological symptoms, or gastrointestinal symptoms (Tables 1 and 2). Pathy (36) demonstrated in 387 elderly patients with acute myocardial infarction that 19% had chest pain, 56% had dyspnea, neurological, or gastrointestinal symptoms, 8% had sudden death, and 17% had other symptoms (Table 2). In 110 elderly patients with acute myocardial infarction, Aronow (29) showed that 21% had no symptoms, 22% had chest pain, 35% had dyspnea, 18% had neurological symptoms, and 4% had gastrointestinal symptoms (Tables 1 and 2).

Table 1  Prevalence of Silent or Unrecognized Q-Wave MI in Elderly Patients

<table>
<thead>
<tr>
<th>Study (reference)</th>
<th>Age (yr)</th>
<th>Unrecognized MI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rodstein (n = 52) (27)</td>
<td>61–92</td>
<td>16</td>
</tr>
<tr>
<td>Aronow et al. (n = 115) (28)</td>
<td>mean, 82</td>
<td>78</td>
</tr>
<tr>
<td>Aronow (n = 110) (29)</td>
<td>mean, 82</td>
<td>23</td>
</tr>
<tr>
<td>Kannel et al. (n = 199 men) (26)</td>
<td>65–94</td>
<td>66</td>
</tr>
<tr>
<td>Kannel et al. (n = 162 women) (26)</td>
<td>65–94</td>
<td>58</td>
</tr>
<tr>
<td>Muller et al. (n = 46 men) (30)</td>
<td>65–95</td>
<td>14</td>
</tr>
<tr>
<td>Muller et al. (n = 67 women) (30)</td>
<td>65–95</td>
<td>34</td>
</tr>
<tr>
<td>Nadelmann et al. (n = 115) (31)</td>
<td>75–85</td>
<td>50</td>
</tr>
<tr>
<td>Sigurdsson et al. (n = 237) (32)</td>
<td>58–62</td>
<td>83</td>
</tr>
<tr>
<td>Sheifer et al. (n = 901) (33)</td>
<td>mean, 72</td>
<td>201</td>
</tr>
</tbody>
</table>

Abbreviation: MI, myocardial infarction.
Other studies have also shown a high prevalence of dyspnea and neurological symptoms in elderly patients with acute myocardial infarction (37–39). In these studies, dyspnea was present in 22% of 87 patients (37), 42% of 777 patients (38), and 57% of 96 patients (39). Neurological symptoms were present in 16% (37), 30% (38), and 34% (39) of patients, respectively. In 777 elderly patients with acute myocardial infarction, Bayer and associates (38) reported that, with increasing age, the prevalence of chest pain decreased whereas the prevalence of dyspnea increased.

In the Multicenter Chest Pain Study, the clinical presentation of acute myocardial infarction was compared in 1615 patients older than 65 years to 5109 younger patients (41). Because of the decreased prevalence in elderly patients of some typical features of acute myocardial infarction present in younger patients, such as pressure-like chest pain, the initial symptoms and signs had a lower predictive value for diagnosing acute myocardial infarction in the older group (41).

Other features that are different between elderly and younger patients with acute myocardial infarction, and which may modify the therapy, need to be emphasized. An important difference is that elderly patients delay longer in seeking medical assistance after the onset of chest pain (42–44). In a study of out-of-hospital chest pain, Tresch and associates (42) reported that elderly patients, 80 years or older, delayed greater than 6.5 hours in calling paramedics, compared with a 3.9 hours delay in patients younger than 70 years. Interestingly, this prolonged delay occurred even though more than 50% of the elderly patients had a past history of either a myocardial infarction or coronary bypass surgery. Such delay may be one of the reasons why elderly patients with acute myocardial infarction are less likely to receive thrombolytic therapy or primary coronary angioplasty compared with younger patients. Sheifer et al. (44) showed in the Cooperative Cardiovascular Project that among 102,339 patients older than 65 years with confirmed acute myocardial infarction, 29.4% arrived at the hospital 6 hours or later after onset of the symptom.

Another important age difference found in Tresch’s study (42), which has been reported in other studies (45,46), was the greater incidence of non-Q-wave myocardial infarctions in the elderly; 40% of elderly patients with acute myocardial infarction demonstrated non-Q-wave infarction compared with only 20% of the younger patients with infarction. Of 91 consecutive patients aged 70 years and older, mean age 78 years, with acute myocardial infarction, 61 (75%) had non-Q-wave myocardial infarction (46).

In younger patients, non-Q-wave myocardial infarctions are usually associated with a more benign acute hospital course than Q-wave myocardial infarctions, although this does not pertain to elderly patients. Chung and associates (47) reported a10% hospital

<table>
<thead>
<tr>
<th>Study (reference)</th>
<th>Age (yr)</th>
<th>Dyspnea</th>
<th>Chest pain</th>
<th>Neurological symptoms</th>
<th>GI symptoms</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rodstein (n = 52) (27)</td>
<td>61–92</td>
<td>10 (19%)</td>
<td>15 (29%)</td>
<td>7 (13%)</td>
<td>3 (6%)</td>
</tr>
<tr>
<td>Pathy (n = 387) (36)</td>
<td>≥65</td>
<td>77 (20%)</td>
<td>75 (19%)</td>
<td>126 (33%)</td>
<td>10 (3%)</td>
</tr>
<tr>
<td>Tinker (n = 87) (37)</td>
<td>mean, 74</td>
<td>19 (22%)</td>
<td>51 (59%)</td>
<td>14 (16%)</td>
<td>0 (0%)</td>
</tr>
<tr>
<td>Bayer et al. (n = 777) (38)</td>
<td>65–100</td>
<td>329 (42%)</td>
<td>515 (66%)</td>
<td>232 (30%)</td>
<td>145 (19%)</td>
</tr>
<tr>
<td>Aronow (n = 110) (29)</td>
<td>mean, 82</td>
<td>38 (35%)</td>
<td>24 (22%)</td>
<td>20 (18%)</td>
<td>5 (4%)</td>
</tr>
<tr>
<td>Wroblewski (n = 96) (39)</td>
<td>mean, 84</td>
<td>57 (59%)</td>
<td>19 (20%)</td>
<td>33 (34%)</td>
<td>24 (25%)</td>
</tr>
</tbody>
</table>

Abbreviations: MI, myocardial infarction; GI, gastrointestinal.
mortality and 36% one-year mortality in a group of elderly patients sustaining acute non-Q-wave myocardial infarction. In contrast, the acute hospital and one-year mortality in younger patients was 3% and 16%, respectively. Moreover, 23% of the elderly patients with non-Q-wave myocardial infarction developed atrial fibrillation, and 53% had congestive heart failure. Regardless of the type of myocardial infarction, elderly patients with acute myocardial infarction usually demonstrate more LV dysfunction than younger patients upon hospital admission and have a more complicated hospital course. Complications are common in elderly patients (48) including heart failure, ventricular rupture, shock, and death; and, not infrequently, the elderly patient’s initial complaints will reflect these complications instead of chest pain.

Fedullo and Swinburne (49) compared complications from acute myocardial infarction in 104 patients aged 70 years and older with 157 patients 70 years or younger. Mortality was 22% in the older group versus 5% in the younger group. Cardiogenic shock occurred in 7% of the older group versus 1% of the younger group. Pulmonary edema occurred in 18% of the older group versus 4% of the younger group. Heart failure occurred in 29% of the older group versus 14% of the younger group. A rhythm disturbance requiring pacemaker implantation occurred in 5% of the older group versus 2% of the younger group (49). The increased mortality and complication rates in older patients with acute myocardial infarction suggest that an aggressive diagnostic and therapeutic approach may be beneficial in these patients (48). More aggressive therapy, including use of aspirin, β-blockers, angiotensin-converting enzyme inhibitors, statins, thrombolytic therapy, and coronary revascularization by percutaneous transluminal coronary angioplasty or by coronary bypass surgery, should be considered (see chap. 11).

**DIAGNOSTIC TECHNIQUES**

**Resting ECG**

In addition to diagnosing recent or previous myocardial infarction, the resting ECG may show ischemic ST-segment depression, arrhythmias, conduction defects, and LV hypertrophy that are related to subsequent coronary events. At 37-month mean follow-up, elderly institutionalized patients with ischemic ST-segment depression 1 mm or greater on the resting ECG were 3.1 times more likely to develop new coronary events (myocardial infarction, primary ventricular fibrillation, or sudden cardiac death) than were those with no significant ST-segment depression (50). In this population, patients with ischemic ST-segment depression 0.5 to 0.9 mm on the resting ECG were 1.9 times more likely to develop new coronary events during the 37-month follow-up than were those with no significant ST-segment depression (50). At 45-month mean follow-up, pacemaker rhythm, atrial fibrillation, premature ventricular complexes, left bundle branch block, intraventricular conduction defect, and type II second-degree atrioventricular (AV) block were all associated with a higher incidence of new coronary events in such elderly patients (51).

Numerous studies have documented that older adults with ECG LV hypertrophy have an increased incidence of new cardiovascular events. Men and women 65 to 94 years of age participating in the Framingham Heart Study who had ECG LV hypertrophy had an increased incidence of new coronary events, atherothrombotic brain infarction, chronic heart failure (CHF), and peripheral arterial disease compared with persons without ECG LV hypertrophy (52). Aronow and associates (53,54) also found that elderly patients with hypertension or CHD and ECG LV hypertrophy had an increased incidence of new coronary events, atherothrombotic brain infarction, and heart failure.
Ambulatory Electrocardiography

Multiple studies have demonstrated that complex ventricular arrhythmias in older adults without underlying cardiovascular disease are not associated with an increased incidence of new coronary events (Table 3) (55–60). In contrast, complex ventricular arrhythmias in elderly persons with underlying cardiovascular disease are associated with an increased incidence of new coronary events, including sudden cardiac death (Table 3) (57–60). The incidence of new coronary events is especially increased in elderly patients with complex ventricular arrhythmias and abnormal LV ejection fraction (58) or LV hypertrophy (59).

Complex ventricular arrhythmias detected by 24-hour AECG in elderly nursing home patients with heart disease predicted a 2.5 times greater incidence of new coronary events at a two-year follow-up in persons with normal LV ejection fraction and 7.6 times greater incidence in those with abnormal LV ejection fraction (Table 3) (60). In elderly persons with heart disease, nonsustained ventricular tachycardia detected by 24-hour AECG was associated with a 3.2 times increased incidence of new coronary events at a two-year follow-up in persons with normal LV ejection fraction, and 6.8-fold higher incidence in those with abnormal LV ejection fraction (Table 3) (59). Those with heart disease, normal LV mass, and complex ventricular arrhythmias detected by 24-hour AECG experienced a 2.4-fold greater incidence of primary ventricular fibrillation or sudden cardiac death at a 27-month follow-up than those without such arrhythmias. This risk was 7.3 times higher in persons with both complex ventricular arrhythmias and echocardiographic LV hypertrophy (Table 3) (60).

AECG performed for 24 hour is also useful in detecting myocardial ischemia in elderly persons with suspected CHD who cannot perform treadmill or bicycle exercise stress testing because of advanced age, intermittent claudication, musculoskeletal disorders, heart failure, or pulmonary disease. Ischemic ST-segment changes demonstrated on the 24-hour AECG correlate with transient abnormalities in myocardial perfusion and LV systolic dysfunction. The changes may be associated with symptoms, or symptoms may be completely absent, which is referred to as SI. SI is predictive of future coronary events, including cardiovascular mortality in older persons with CHD (19–21,62–66) and in those with no clinical heart disease (21,55,67) (Table 4).

The incidence of new coronary events is especially increased in elderly individuals with SI plus complex ventricular arrhythmias (62), abnormal LV ejection fraction (20), or echocardiographic LV hypertrophy (68). In a population of institutionalized elderly with CHD or hypertension, at a 40-month follow-up, SI predicted a doubled incidence of new coronary events in persons with normal LV ejection fraction and a 3.2-fold increase in those with abnormal LV ejection fraction (Table 4) (20). The combination of complex ventricular arrhythmias plus SI was associated with a fourfold higher incidence of new coronary events (Table 4) (20); echocardiographic LV hypertrophy plus SI predicted a 3.4-fold greater incidence of new coronary events at a 31-month follow-up (68). SI was associated with approximately a doubled incidence of new coronary events over nearly four years of follow-up in both elderly men and women with CHD, hypertension, valvular heart disease, or cardiomyopathy. Among those without clinical heart disease, SI predicted an incidence of new coronary events 6.3-fold higher in men and 4.4-fold higher in women (Table 4) (67).

Hedblad and associates (21) showed at a 43-month follow-up that SI predicted a 16-fold higher incidence of new coronary events in men with CHD and a 4.4-fold higher event rate in men without CHD (Table 4). Fleg and associates (55) showed at a 10-year follow-up of elderly persons without heart disease that SI was associated with a 3.8-fold
### Table 3  Association of Complex Ventricular Arrhythmias and Ventricular Tachycardia with New Coronary Events in Elderly Patients

<table>
<thead>
<tr>
<th>Study (reference)</th>
<th>Mean age (yr)</th>
<th>Cardiac status</th>
<th>Follow-up (mo)</th>
<th>Incidence of new coronary events</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fleg et al. ((n = 98)) (55)</td>
<td>69</td>
<td>No heart disease</td>
<td>120</td>
<td>No association</td>
</tr>
<tr>
<td>Kirkland et al. ((n = 30)) (56)</td>
<td>79</td>
<td>No heart disease</td>
<td>29</td>
<td>No association</td>
</tr>
<tr>
<td>Aronow et al. ((n = 843)) (58)</td>
<td>82</td>
<td>Heart disease</td>
<td>39</td>
<td>Increased 1.7 times by complex VA</td>
</tr>
<tr>
<td>Aronow et al. ((n = 391)) (59)</td>
<td>82</td>
<td>Heart disease</td>
<td>24</td>
<td>With normal LVEF, increased 2.5 times by complex VA and 3.2 times by VT; increased 7.6 times by complex VA plus abnormal LVEF and increased 6.8 times by VT plus abnormal LVEF</td>
</tr>
<tr>
<td>Martin et al. ((n = 106)) (57)</td>
<td>75–95</td>
<td>No heart disease</td>
<td>60</td>
<td>Total mortality increased 1.9 times by frequent VA</td>
</tr>
<tr>
<td>Aronow et al. ((n = 468)) (60)</td>
<td>82</td>
<td>Heart disease</td>
<td>27</td>
<td>With no LVH, SCD or VF increased 2.4 times by complex VA and 1.8 times by VT; SCD or VF increased 7.3 times by complex VA plus LVH and increased 7.1 times by VT plus LVH</td>
</tr>
</tbody>
</table>

| Aronow et al. \((n = 395\) men) (61) | 80 | CAD | 45 | Increased 2.4 times by complex VA and 1.7 times by VT |
| Aronow et al. \((n = 385\) men) (61) | 80 | HT, VD, or CMP | 45 | Increased 1.9 times by complex VA and 1.9 times by VT |
| Aronow et al. \((n = 135\) men) (61) | 80 | No heart disease | 45 | No association |
| Aronow et al. \((n = 771\) women) (61) | 81 | CAD | 47 | Increased 2.5 times by complex VA and 1.7 times by VT |
| Aronow et al. \((n = 806\) women) (61) | 81 | HT, VD, or CMP | 47 | Increased 2.2 times by complex VA and 2.0 times by VT |
| Aronow et al. \((n = 297\) women) (61) | 81 | No heart disease | 47 | No association |

**Abbreviations:** VA, ventricular arrhythmias; VT, ventricular tachycardia; LVEF, left ventricular ejection fraction; LVH, left ventricular hypertrophy; SCD, sudden coronary death; VF, primary ventricular fibrillation; CAD, coronary artery disease; HT, hypertension; VD, valvular heart disease; CMP, cardiomyopathy.
### Table 4  Association of SI with New Coronary Events in Elderly Patients

<table>
<thead>
<tr>
<th>Study (reference)</th>
<th>Mean age (yr)</th>
<th>Cardiac status</th>
<th>Follow-up (mo)</th>
<th>Incidence of new coronary events</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fleg et al. (n = 98)</td>
<td>69</td>
<td>No heart disease</td>
<td>120</td>
<td>Increased 3.8 times by SI</td>
</tr>
<tr>
<td>Aronow et al. (n = 393)</td>
<td>82</td>
<td>CAD or HT</td>
<td>40</td>
<td>Increased 2.0 times by SI; increased 2.4 times by SI with normal LVEF; increased 3.2 times by SI with abnormal LVEF</td>
</tr>
<tr>
<td>Aronow et al. (n = 404)</td>
<td>82</td>
<td>CAD or HT</td>
<td>37</td>
<td>Increased 2.0 times by SI; increased 4.0 times by SI plus complex VA; increased 2.5 times by SI plus VT</td>
</tr>
<tr>
<td>Hedblad et al. (n = 39 men)</td>
<td>68</td>
<td>CAD</td>
<td>43</td>
<td>Increased 16.0 times by SI</td>
</tr>
<tr>
<td>Hedblad et al. (n = 385 men)</td>
<td>68</td>
<td>No CAD</td>
<td>43</td>
<td>Increased 4.4 times by SI</td>
</tr>
<tr>
<td>Aronow et al. (n = 395 men)</td>
<td>80</td>
<td>CAD</td>
<td>45</td>
<td>Increased 2.1 times by SI</td>
</tr>
<tr>
<td>Aronow et al. (n = 385 men)</td>
<td>80</td>
<td>HT, VD, or CMP</td>
<td>45</td>
<td>Increased 1.8 times by SI</td>
</tr>
<tr>
<td>Aronow et al. (n = 135 men)</td>
<td>80</td>
<td>No heart disease</td>
<td>45</td>
<td>Increased 6.3 times by SI</td>
</tr>
<tr>
<td>Aronow et al. (n = 771 women)</td>
<td>81</td>
<td>CAD</td>
<td>47</td>
<td>Increased 2.1 times by SI</td>
</tr>
<tr>
<td>Aronow et al. (n = 806 women)</td>
<td>81</td>
<td>HT, VD, or CMP</td>
<td>47</td>
<td>Increased 1.7 times by SI</td>
</tr>
<tr>
<td>Aronow et al. (n = 297 women)</td>
<td>81</td>
<td>No heart disease</td>
<td>47</td>
<td>Increased 4.4 times by SI</td>
</tr>
</tbody>
</table>

**Abbreviations:** SI, silent myocardial ischemia; CAD, coronary artery disease; HT, hypertension; LVEF, left ventricular ejection fraction; VA, ventricular arrhythmias; VT, ventricular tachycardia; VD, valvular heart disease; CMP, cardiomyopathy.
increased incidence of new coronary events (Table 4); two of the three persons who died suddenly had evidence of SI plus ventricular tachycardia detected by 24-hour AECG.

SI detected by 24-hour AECG has been used in the assessment of patients undergoing nocardiac surgery. Such use of 24-hour AECG may be especially beneficial in elderly persons, who are frequently at high surgical risk and may not be able to undergo preoperative exercise stress testing because of concomitant illness. No study, however, has shown SI detected by 24-hour AECG to be more accurate than pharmacological stress testing in stratifying preoperative elderly patients into high- and low-risk groups.

Raby and associates (69) studied 176 patients who underwent 24-hour AECG before noncardiac surgery. Eighteen percent of the patients had signs of myocardial ischemia on their preoperative 24-hour AECG, with the ischemia silent in the majority of patients. Preoperative myocardial ischemia was highly predictive of postoperative cardiac events. The sensitivity of preoperative myocardial ischemia for postoperative cardiac events in this study was 92%, the specificity 88%, the positive predictive value 38%, and the negative predictive value 99% (69). Multivariate analysis showed preoperative myocardial ischemia to be the most significant variable correlating with postoperative cardiac events. The authors concluded that the absence of preoperative myocardial ischemia on the 24-hour AECG indicates a very low risk for postoperative cardiac events. Thirty-eight percent of the patients in this study were older than 69 years, and preoperative myocardial ischemia was more prevalent in these elderly patients compared with the younger patients.

In a follow-up study, Raby and associates (70) assessed the significance of intraoperative and postoperative SI in addition to preoperative ischemia detected on a 24-hour AECG in relationship to postoperative cardiac events in patients undergoing peripheral vascular surgery. The mean age of the patients in this study was 67 years, and 37% were 70 years or older. As in their previous study, the investigators found preoperative SI to be the most important predictor of postoperative cardiac events. Preoperative myocardial ischemia also strongly correlated with intraoperative and postoperative ischemia, and perioperative myocardial ischemia commonly preceded clinical cardiac events (70).

**Signal-averaged Electrocardiography**

Signal-averaged electrocardiography (SAECG) was performed in 121 elderly post-infarction patients with asymptomatic complex ventricular arrhythmias detected by 24-hour AECG and a LV ejection fraction greater than or equal to 40% (71). At 29-month follow-up, the sensitivity, specificity, positive predictive value, and negative predictive value for predicting sudden cardiac death were 52%, 68%, 32%, and 83%, respectively, for a positive SAECG; 63%, 70%, 38%, and 87%, respectively, for nonsustained ventricular tachycardia; and 26%, 89%, 41%, and 81%, respectively, for a positive SAECG plus nonsustained ventricular tachycardia (71).

**Echocardiography**

Echocardiography is useful in detecting regional LV wall motion abnormalities, acute myocardial ischemia, and complications secondary to acute myocardial infarction, LV aneurysm, cardiac thrombi, left main CAD, LV hypertrophy, and associated valvular heart disease. Echocardiography is useful in evaluating LV function and cardiac chamber size in elderly persons with CHD. Echocardiographic LV ejection fraction is also important in predicting new coronary events in elderly persons with CHD (20,59,72).
New coronary events developed at a two-year follow-up in 30 of 45 elderly nursing home patients with CHD and abnormal LV ejection fraction (<50%) and in 24 of 90 such patients with CHD and normal LV ejection fraction (relative risk = 2.5) (59). In this population of older adults with CHD and heart failure, cardiovascular mortality is higher among individuals with abnormal than those with normal LV ejection fraction (72,73). Multivariate analysis showed that LV ejection fraction was the most important prognostic variable for mortality in elderly persons with CHF associated with CHD; those with abnormal LV ejection fraction had approximately twice the mortality of persons with normal LV ejection fraction (72,73).

Numerous studies have demonstrated that elderly patients with echocardiographic LV hypertrophy have an increased incidence of new cardiovascular events (53,54,60,68,74,75). At four-year follow-up, elderly men and women in the Framingham Study with echocardiographic LV hypertrophy had a relative risk for new coronary events of 1.67 for men and of 1.60 for women per 50 g/m increase in LV mass/height (Table 5) (74). In these volunteers, echocardiographic LV hypertrophy was 15.3 times more sensitive than ECG LV hypertrophy in predicting new coronary events in elderly men and 4.3 times more sensitive than ECG LV hypertrophy in predicting new coronary events in elderly women (74).

Over 27 months of follow-up, institutionalized elderly adults with echocardiographic LV hypertrophy developed a 2.7-fold higher incidence of new coronary events, 3.7-fold higher rate of new atherothrombotic brain infarction (ABI), and 3.3-fold greater rate of primary ventricular fibrillation or cardiac death (Table 5) (60). At a 37-month follow-up of elderly persons with CHD or hypertension, echocardiographic LV hypertrophy predicted a doubled incidence of new coronary events and a 2.8-fold greater rate of new ABI (Table 5) (53). Echocardiographic LV hypertrophy was approximately four times more sensitive than ECG LV hypertrophy in predicting new coronary events or new ABI in this population (53). Multiple logistic regression analysis showed that echocardiographic

<table>
<thead>
<tr>
<th>Population (reference)</th>
<th>Mean age (yr)</th>
<th>Follow-up (yr)</th>
<th>Incidence of new cardiovascular events</th>
</tr>
</thead>
<tbody>
<tr>
<td>Framingham Study</td>
<td>65–94</td>
<td>4</td>
<td>Coronary events increased 1.67 times per 50 g/m increase in LV mass/height</td>
</tr>
<tr>
<td>(n = 406 men) (74)</td>
<td></td>
<td></td>
<td>Coronary events increased 1.60 times per 50 g/m increase in LV mass/height</td>
</tr>
<tr>
<td>Framingham Study</td>
<td>65–94</td>
<td>4</td>
<td>LVH increased coronary events 2.7 times and ABI 3.7 times</td>
</tr>
<tr>
<td>(n = 735 women) (74)</td>
<td></td>
<td></td>
<td>LVH increased coronary events 2.0 times and ABI 2.8 times</td>
</tr>
<tr>
<td>Cardiovascular disease</td>
<td>82</td>
<td>2.3</td>
<td>LVH increased primary ventricular fibrillation or sudden cardiac death 3.3 times</td>
</tr>
<tr>
<td>(n = 557) (75)</td>
<td></td>
<td></td>
<td>LV increased coronary events 3.3 times, ABI 2.8 times, and CHF 3.7 times</td>
</tr>
<tr>
<td>Hypertension or CHD</td>
<td>82</td>
<td>3.1</td>
<td>LV increased coronary events 2.7 times, ABI 3.3 times, and CHF 3.5 times</td>
</tr>
<tr>
<td>(n = 360) (59)</td>
<td></td>
<td></td>
<td>LV increased coronary events 2.7 times, ABI 3.3 times, and CHF 3.5 times</td>
</tr>
<tr>
<td>Heart disease</td>
<td>82</td>
<td>2.3</td>
<td>LVH increased primary ventricular fibrillation or sudden cardiac death 3.3 times</td>
</tr>
<tr>
<td>(n = 468) (60)</td>
<td></td>
<td></td>
<td>LV increased coronary events 3.3 times, ABI 2.8 times, and CHF 3.7 times</td>
</tr>
<tr>
<td>African-Americans with hypertension</td>
<td>78</td>
<td>3.1</td>
<td>LV increased coronary events 3.3 times, ABI 2.8 times, and CHF 3.7 times</td>
</tr>
<tr>
<td>(n = 84) (54)</td>
<td></td>
<td></td>
<td>LV increased coronary events 2.7 times, ABI 3.3 times, and CHF 3.5 times</td>
</tr>
<tr>
<td>Whites with hypertension</td>
<td>82</td>
<td>3.6</td>
<td>LV increased coronary events 2.7 times, ABI 3.3 times, and CHF 3.5 times</td>
</tr>
</tbody>
</table>

Abbreviations: LVH, left ventricular hypertrophy; CHD, coronary heart disease; ABI, atherothrombotic brain infarction; CHF, chronic heart failure.
LV hypertrophy was a strong independent risk factor in such a population for new coronary events (odds ratio of 3.2), new ABI (odds ratio of 4.2), and new CHF (odds ratio of 2.6) (54); increased risk was similar in African-Americans and whites (Table 5).

Exercise and Pharmacological Stress Testing

Although age per se significantly influences the cardiovascular response to aerobic exercise, treadmill or cycle ergometer exercise testing remains a useful diagnostic and prognostic tool for evaluating older patients with suspected or documented CHD. Exercise ECG is also a useful prognostic indicator of subsequent coronary events in patients with documented CHD, with or without previous myocardial infarction. Exercise testing in elderly patients should evaluate symptoms that develop during exercise (especially angina pectoris or dyspnea, which may be an anginal equivalent), the maximal workload achieved, the heart rate and blood pressure response, the presence, magnitude, and onset time of ischemic ST-segment depression or elevation, and the presence of exercise-induced arrhythmias. These variables must be interpreted in light of normative age-associated changes including a decline of maximal aerobic capacity averaging 8% to 10% per decade (76,77), a reduced maximal heart rate of approximately 1 beat/min/yr, and an exaggerated rise in systolic blood pressure (78,79). Maximal LV systolic emptying is impaired in older adults, resulting in a higher end-systolic volume and lower ejection fraction compared with younger individuals (78–80); stroke volume is preserved, however, by a greater reliance on the Frank-Starling mechanism to augment LV end-diastolic volume (79,80). Exercise-induced supraventricular (81) and ventricular arrhythmias (82) both increase exponentially with age in clinically healthy volunteers but do not increase the risk for future CHD events in such a population.

Given the cardiovascular and noncardiovascular limitations to exercise in older adults, exercise-testing protocols should employ low starting work rates and smaller work increments than in younger patients. Thus, protocols such as the Naughton or Balke, in which the speed is held constant and only the elevation is increased, are ideal for the elderly. Individuals with gait disturbances can often be tested on a cycle ergometer, although their aerobic capacity and peak heart rate are usually lower than those achieved with treadmill exercise.

Diagnostic sensitivity of the exercise ECG for CHD appears to increase with age at the expense of a modest reduction in specificity. Hlatky et al. (83) found the exercise ECG to have a sensitivity of 84% and a specificity of 70% for the diagnosis of CHD in patients 60 years or older. In contrast, sensitivity was only 56% in patients younger than 40 years, although specificity was 84%. In patients aged 65 years and older, Newman and Phillips (84) found a sensitivity of 85%, a specificity of 56%, and a positive predictive value of 86% for the exercise ECG in diagnosing CHD. The increased sensitivity and high positive predictive value of the exercise ECG with increasing age found in these two treadmill exercise studies was probably due to the increased prevalence and severity of CHD in elderly persons (85). Reduced specificity is largely explained by a higher prevalence of ST-T-wave abnormalities on the pre-exercise ECG.

Prognostic Utility of the Exercise ECG

Numerous studies in patients with known or suspected CHD have shown that the standard treadmill exercise test provides valuable prognostic information. In a sample of 2632 patients 65 years or older undergoing clinically indicated exercise testing, a lower peak treadmill workload was a strong independent predictor of cardiac death
over the subsequent 2.9-year mean follow-up period (86). Of note, neither ischemic ST changes nor angina were predictive. In a similar population, however, Glover et al., demonstrated that an ischemic ST-segment response to exercise predicted an eightfold cardiovascular mortality (17% vs. 2%) over a two-year follow-up (87). The Duke treadmill score, which incorporates exercise duration, magnitude of ischemic ST-segment depression, and presence of exercise-induced angina, has demonstrated prognostic utility in younger populations (88,89), but appears to be less useful in patients aged 75 years or older (89).

Exercise testing after myocardial infarction has prognostic value in older patients, as it does in younger ones. Identification of jeopardized myocardium in such post-myocardial infarction patients may be useful because recurrent infarction and sudden cardiac death are the most common causes of one-year mortality posthospital discharge (90). In 188 patients aged 70 years or older who underwent exercise testing a mean of 14 days’ postinfarction, Ciaroni et al. (91) found that a rise in systolic blood pressure of less than 30 mmHg, a maximal cycle workrate less than 60 W, and an exercise duration less than 5 minutes predicted cardiovascular death; whereas ST-segment depression and ventricular arrhythmias predicted reinfarction and the need for coronary revascularization. Similar to the general postinfarction population, older patients excluded from exercise testing after myocardial infarction have the highest cardiovascular risk. For example, Deckers et al. (92) found a mortality of 4% for patients 65 years or older who were able to perform a cycle exercise test postinfarction versus a mortality of 37% for those excluded.

Although the diagnostic and prognostic utility of exercise testing in general population is modest, such testing may have greater value in asymptomatic older persons with multiple CHD risks factors (93). Older subjects embarking on a vigorous training program or those entrusted with the safety of others, such as school bus drivers, are appropriate candidates for testing.

Exercise Cardiac Imaging
Exercise stress testing incorporating thallium perfusion scintigraphy, radionuclide ventriculography, or echocardiography provides additional value in the diagnosis and prognosis of CHD compared with the exercise ECG alone. Iskandrian et al. (94) showed that exercise thallium-201 imaging can be used for risk stratification of elderly patients with CHD. The risk for cardiac death or nonfatal myocardial infarction at a 25-month follow-up in 449 patients 60 years or older was less than 1% in patients with normal images, 5% in patients with single-vessel thallium-201 abnormality, and 13% in patients with multivessel thallium-201 abnormality. In 120 patients 70 years or older with known or suspected CHD who underwent exercise thallium-201 scintigraphy, Hilton et al. (95) showed that the combination of low peak exercise capacity and any thallium-201 perfusion defect was the most powerful predictor of new cardiac events (relative risk, 5.3 at 1 year). Individuals with an ischemic ST-segment depression more than 2 mm and a thallium defect who failed to complete stage 1 of a Bruce protocol suffered a 47% event rate. Exercise single-photon emission computed tomography (SPECT) was performed in 247 elderly patients aged 75 years and older (108 women and 139 men) and classified 49% of the patients as low risk and 35% of the patients as high risk by a summed stress score (96). At 6.4-year follow-up, patients classified as low risk had an annual cardiac mortality rate of 0.8%, and those classified as high risk had an annual cardiac mortality rate of 5.8%. In this study, the Duke treadmill score was not significantly associated with cardiac death (96).
Fleg et al. (5) performed maximal treadmill exercise ECGs and thallium scintigraphy in 407 asymptomatic volunteers aged between 40 to 96 years from the Baltimore Longitudinal Study on Aging. At 4.6 years of follow-up, new cardiac events developed in 7% of patients who had negative results on both tests, 8% of patients with a single positive result, and 48% of patients with both results positive. Persons with both a positive exercise ECG and a thallium perfusion defect averaged 69 years of age and had 3.6 times the relative risk for new coronary events as those with negative results, independent of standard coronary risk factors (5).

Echocardiography during, or more commonly, immediately after treadmill or cycle exercise has also proven useful in the detection and prognostication of CHD. Overall sensitivity of exercise-induced wall motion abnormalities for CHD using this technique is 74–97% with specificity of 64–88%, similar to values of exercise thallium scintigraphy (97,98). As with other diagnostic modalities, the sensitivity of exercise echocardiography increases with the extent of CHD, which should result in a high sensitivity in the elderly. Although a lower technical success of echocardiographic imaging in older versus younger patients is probably responsible for a lesser utilization of exercise echocardiography in the elderly, recent advances in echocardiographic equipment have largely overcome this deficiency. In 2632 patients, aged 65 years or older, referred for clinically indicated exercise echocardiography, the exercise-induced changes in LV end-systolic volume and the exercise LV ejection fraction or wall motion score were predictors of cardiac events and cardiac death, independent of clinical status, resting echocardiography, and exercise duration (86) (Fig. 2).

At 2.8-year follow-up of 1268 patients of mean age 60 years, nonfatal myocardial infarction or cardiac death occurred in 1.1% patients per year with a normal stress echocardiogram and in 3.6% patients per year with a normal stress ECG (p < 0.001) (99). Peak wall motion score index (hazard ratio = 2.55) and LV ejection fraction (hazard ratio = 0.99) were independent and incremental prognostic markers for stress echocardiography (99).

Figure 2 Exercise echocardiographic wall motion score as a predictor of survival free of cardiac events in 2632 patients aged 65 years or older referred for exercise testing. A higher wall motion score index (WMSI) denotes worse LV function. Source: From Ref. 86.
Older patients with diabetes mellitus (mean age 63 years) had a significantly higher prevalence of unrecognized myocardial infarction (18% of 287 patients) detected by a treadmill exercise sestamibi stress test than age-matched and gender-matched patients without diabetes mellitus (7% of 292 patients) ($p < 0.001$) (100). Patients with diabetes mellitus also had a higher prevalence of SI without a history of angina pectoris (33%) than patients without diabetes mellitus (18%) ($p < 0.001$) (100).

Pharmacological Stress Testing

The greatest advancement in stress testing over the past decade has been the widespread application of pharmacological stress testing on populations unable to perform diagnostically adequate exercise tests. The elderly are clearly the greatest beneficiaries of pharmacological stress testing because of the high prevalence of exercise-limiting conditions among them, such as obstructive lung disease, peripheral arterial insufficiency, arthritis, and neuromuscular disorders. The agents most commonly used for this purpose are the vasodilators, dipyridamole and adenosine, and the synthetic catecholamine, dobutamine, in conjunction with either radionuclide or echocardiographic imaging.

Dipyridamole is a phosphodiesterase inhibitor that blocks degradation of adenosine, thereby increasing plasma adenosine, which is a potent arteriolar dilator. Both dipyridamole and adenosine dilate normal coronary arteries more than stenotic vessels, creating a coronary steal that causes a myocardial perfusion defect or wall motion abnormality. With either drug, serious side effects, including bronchospasm, hypotension, and arrhythmias, occur in 2–3% of patients but do not appear to be age-related (101–103). In 101 subjects older than 70 years, the sensitivity and specificity of dipyridamole thallium imaging for CHD were 86% and 75%, respectively, compared with corresponding values of 83% and 70% in younger patients (102). In 92 patients aged 65 years and older who had undergone prior coronary artery bypass grafting, the dipyridamole sestamibi stress test had a sensitivity of 95%, a specificity of 50%, a positive predictive value of 96%, and a negative predictive value of 43% for graft occlusion or 50% or more new native CAD (108); these values were similar to those in younger patients (104).

Prognostic utility of dipyridamole in combination with echocardiography was shown in 190 patients aged 65 years and above (mean, 68 ± 3), evaluated at a mean of 10 days after uncomplicated myocardial infarction. Patients with a positive test experienced a threefold risk of future cardiac events and 4.4-fold risk of death compared with those with negative, i.e., normal results (105). An abnormal dipyridamole thallium scan was the best predictor of subsequent events in 348 patients aged 70 years and older with known or suspected CHD conferring a relative risk of 7.2 on multivariate analysis (106). Dipyridamole stress imaging has also been used to identify patients at high cardiovascular risk prior to vascular surgery. Hendel et al. (107) observed that a reversible thallium perfusion defect conferred a ninefold risk of perioperative myocardial infarction or cardiac death in 360 such patients whose mean age was 65 years.

Adenosine echocardiography has also demonstrated both diagnostic and prognostic utility in older patients with known or suspected CHD. In 120 such patients 70 years or older, sensitivity for CHD was 66%, specificity 90%, and diagnostic accuracy 73% (103). Sensitivity increased from 42% in patients with single-vessel CHD to 73% in those with multivessel disease. An abnormal adenosine echocardiogram predicted a threefold risk of future cardiac events, independent of clinical CHD risk factors. The only serious effect was transient AV block, which occurred in 6% of patients, but was asymptomatic and self limited in all (103). In another study, the risk of such transient AV block after adenosine infusion was 18% in patients 75 years or older versus 8% in younger patients (108).
Combining adenosine infusion with symptom-limited treadmill exercise reduced the incidence of premature infusion termination from 15% to 5%.

A potential advantage of adenosine, and probably dipyridamole, stress testing over exercise is the ability to continue β-blockers without compromising on diagnostic yield. In a study of 158 consecutive patients (mean age 66 years) who had adenosine SPECT myocardial perfusion imaging, β-blocker therapy was continued through the test in 82 patients and stopped 48 hours prior to the test in 76 patients (109). β-Blocker therapy did not affect the extent, severity, and reversibility of perfusion defects on adenosine SPECT myocardial perfusion imaging. However, patients who stopped β-blockers for 48 hours had a higher incidence of angina pectoris (10%) than those who continued β-blocker therapy through the test (2%) (109).

Dobutamine is a synthetic catecholamine that is frequently used as a pharmacological stressor in older patients, in combination with echocardiography or thallium imaging. Dobutamine produces dose-related increases in heart rate and inotropy that augment coronary artery blood flow, thereby inducing ischemia by a mechanism similar to exercise in patients with CHD. Atropine is frequently combined with dobutamine to help ensure an adequate chronotropic response. The classic ischemic response induced by dobutamine is characterized by improved wall motion at low doses but worsening wall motion at high doses. Dobutamine is particularly useful in older patients with obstructive lung disease, in whom both dipyridamole and adenosine are contraindicated. In 120 patients aged 70 years or older with known or suspected CHD, dobutamine echocardiography had a sensitivity of 87%, a specificity of 84%, and an accuracy of 86%, all higher than corresponding figures for adenosine in the same patients (Table 6) (103). Patients with a positive dobutamine stress test had a 7.3-fold risk for a future cardiac event compared with those with a normal test. Dobutamine thallium scintigraphy demonstrated sensitivity of 86% and specificity of 90% in 144 patients aged 65 ± 10 years (110), numbers very similar to the echocardiographic data with this drug. Dobutamine has also been used to predict perioperative coronary events in older patients undergoing vascular surgery (111). Although dobutamine is generally well tolerated in all age groups, higher rates of asymptomatic hypotension and both supraventricular and ventricular arrhythmias, but a lower rate of chest pain, were reported in patients older versus younger than 70 years (112,113).

Several large series have confirmed the prognostic value of dobutamine stress testing. At 6.5-year follow-up of 1434 patients older than 65 years who had dobutamine stress echocardiography, resting wall abnormalities (hazard ratio = 1.13) and inducible ischemia (hazard ratio = 2.1) were significant independent predictors of

<table>
<thead>
<tr>
<th>Table 6</th>
<th>Comparison of Dobutamine and Adenosine Echocardiography in Detection of CAD in Patients Aged 70 Years or Older</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Dobutamine (%)</td>
</tr>
<tr>
<td>Sensitivity</td>
<td>Overall</td>
</tr>
<tr>
<td>1-vessel CHD</td>
<td>74</td>
</tr>
<tr>
<td>2-vessel CHD</td>
<td>88</td>
</tr>
<tr>
<td>3-vessel CHD</td>
<td>91</td>
</tr>
<tr>
<td>Specificity</td>
<td>84</td>
</tr>
<tr>
<td>Accuracy</td>
<td>86</td>
</tr>
</tbody>
</table>

Abbreviations: CHD, coronary heart disease; NS, not significant.
Source: Adapted from Ref. 97.
cardiac death or nonfatal myocardial infarction (114). At 2.6-year follow-up of 7333 patients, mean age 59 years, who had stress echocardiography with either dipyridamole or dobutamine, the cardiac mortality was 29% in patients with a positive test versus 8% in those with a negative test (115). Older age remained a strong independent predictor of cardiac death. Among 931 patients (mean age 61 years) with inducible myocardial ischemia during dobutamine stress echocardiography, ischemia was silent in 69% and symptomatic in 31% (116). At 5.5-year follow-up, cardiac death or nonfatal myocardial infarction occurred in 3% of patients with symptomatic myocardial ischemia and in 4.6% of patients with SI ($p < 0.01$). SI predicted a 70% higher risk of cardiac death or nonfatal myocardial infarction, perhaps because such patients were less likely to be treated with cardioprotective therapy and coronary revascularization than patients with symptomatic myocardial ischemia (116).

**Multislice Computed Tomography and Magnetic Resonance Imaging**

Over the past several years, multislice computed tomography (MSCT) and magnetic resonance imaging (MRI) have become increasingly used to detect CHD. Both techniques allow direct visualization of the coronary arteries rather than relying on their functional consequences. Since their introduction for coronary artery imaging in 2000, CT scanners have increased from 4 to 16 detectors and more recently to 64 detectors. Thus, new generation scanners acquire more imaging slices per rotation, allowing faster image acquisition and improved temporal and spatial resolution. As a result, these scanners require a shorter period of breath holding by the patient, allow a wider range of acceptable heart rates, and the ability to image very obese patients and those with moderate coronary artery calcium, using lower contrast volumes. All of these advances in CT imaging facilitate the imaging of older patients with suspected CHD.

A recent meta-analysis of results with 4, 8, and 16 slice scanners revealed a per artery sensitivity of 85% and specificity of 95% (117). It should be noted, however, that the mean age of patients in the 24 studies included ranged from 56 to 65 years; no separate analyses were performed in the elderly. In another pooled analysis, MSCT detected occluded coronary artery bypass grafts with a sensitivity of 84% and a specificity of 95% (118). Artifacts from metal surgical clips remain an important limitation of MSCT for this use; approximately, only 80% of grafts can be evaluated. Significant drawbacks of MSCT are the contrast dye load and the radiation exposure, both similar to those from conventional coronary angiography.

Cardiac MRI has also become an attractive method for noninvasive coronary artery imaging in recent years. This technique avoids the use of ionizing radiation and iodinated intravenous contrast material as well as the need for breath holding. Faster MRI techniques and more powerful magnets have improved the quality of coronary arterial images. A meta-analysis of 28 studies using MRI coronary angiography found a per-artery sensitivity of 72% and a specificity of 87%; 86% of the coronary arterial segments were assessable (117). However, the mean age of the patients in this analysis was 63 years, with only one very small study having a mean patient age over 65 years. As with MSCT, therefore, age-specific diagnostic accuracy is not available.

Dewey et al. performed a direct comparison of MSCT with MRI for noninvasive coronary arteriography in 129 patients (mean age, 64 years) with suspected CHD (119). Sensitivity for coronary stenoses greater than 50% of luminal diameter was 82% for MSCT versus 54% for MRI; the respective specificities were 90% and 87%. Negative predictive value was slightly higher for CT (95% vs. 90%). In this study, 74% of patients...
preferred MSCT to MRI. The greater diagnostic accuracy of MSCT over MRI in this study is consistent with the meta-analytic findings noted above. Thus, MSCT currently has a higher accuracy than MRI to detect or exclude significant CHD, although data specific to the elderly are lacking. As both techniques may miss significant coronary artery stenoses, they are best used in patients with a pretest probability of CHD less than 50%. In such patients, a normal coronary arteriogram by MSCT or MRI would reduce the posttest probability of CHD to less than 10%, avoiding the need for invasive coronary arteriography (119,120). Both techniques are thus attractive for use in emergency room settings in determining which low-to-intermediate risk patients presenting with acute chest pain should be admitted.

Coronary Arteriography

Despite the recent advances in noninvasive cardiac imaging discussed above, invasive coronary arteriography remains the accepted standard for detection and quantitation of CHD, although it may underestimate the extent of coronary atherosclerosis compared with intravascular ultrasound. Major complications of coronary arteriography include myocardial infarction, stroke, and death. In the Coronary Artery Surgery Study (CASS) registry, each of these endpoints was approximately three times as common in patients aged 65 and above than in younger individuals (6). A single center study between 1980 and 1990 in 242 patients 80 to 92 years old reported a mortality of 0.8% and nonfatal complication rate of 5%, compared with respective rates of 0.15% and 1.5% in patients younger than 80 years (121). The increased risk in the elderly is largely explained by their generally greater severity of underlying cardiac and noncardiac disease. Although major complication rates from cardiac catheterization and coronary arteriography continued to decline through the 1990s (122), the elderly should still be considered at higher risk, especially those aged 80 years and beyond.

REFERENCES

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10
Angina in the Elderly

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INTRODUCTION

Coronary artery disease (CAD) is the number one cause of death in elderly patients and also the major cause of hospitalization and rehospitalizations in this age group. Clinically, CAD manifests as both acute and chronic ischemic syndromes, and it is important that the practicing physician have an understanding of the pathophysiology of these syndromes, as well as confidence in management of these in elderly patients. This chapter will discuss the evaluation and management of elderly patients who demonstrate two of these ischemic syndromes—stable and unstable angina.

Recent advances in cellular and molecular biology have provided a better understanding of coronary atherosclerosis, the underlying disease process causing myocardial ischemia. Because of these advances and the development of new therapies, we are now not only able to relieve the patient’s symptoms, but are also able to modify the underlying pathophysiology.

Evaluation and treatment of myocardial ischemia in elderly patients pose unique challenges to the physician. Although the pathophysiology of myocardial ischemia and the treatment options are similar in elderly and younger patients, there are significant differences in the presentation and response to treatment between these age groups. Elderly CAD patients with myocardial ischemia often present with “atypical” symptoms, and have more comorbid illnesses, greater number of vessels involved, and worse left ventricular (LV) function (1–6). The pharmacokinetics of medications is altered in elderly patients, and there is often a greater sensitivity to medication and greater potential for side effects and drug-drug interactions. Since elderly patients often present with more advanced CAD and their prognosis is often worse, there is greater potential for gain from aggressive interventions, such as angioplasty [percutaneous transluminal coronary angioplasty (PTCA)] and bypass surgery [coronary artery bypass grafting (CABG)], although the risks are greater compared with younger patients. Finally, elderly patients
and their families may place different values on risk, quality of life, and the importance of prognosis, all of which must be considered by the practicing physician.

**EVALUATION AND MANAGEMENT**

The most common symptom of myocardial ischemia in elderly patients as well as in younger patients is exertional chest pain (angina); however, in many older patients, instead of chest pain, exertional dyspnea may be the initial manifestation of ischemia. Other common symptoms experienced by elderly patients with myocardial ischemia are dizziness, mental confusion, or easy fatigability. In some elderly patients with myocardial ischemia, the presentation will be the sudden onset of heart failure ("flash" pulmonary edema) (7–9) or arrhythmias, including sudden death (10). Silent ischemia is particularly common in elderly patients with CAD, occurring in up to one-third of elderly patients, as documented by ambulatory ECG monitoring (11,12).

The initial evaluation of the elderly patient with possible myocardial ischemia should begin with a thorough history and complete physical examination, and determination of coronary risk factors and comorbid illnesses. The assessment should determine if the patient is stable or unstable and the risk stratification of the patient. In addition to advanced age, morbidity and mortality in elderly patients with acute myocardial ischemia are directly related to LV function, extent of CAD, and presence of comorbidity. During the evaluation, the physician caring for elderly patients with myocardial ischemia will need to consider the effects of the disease on the whole person (including physical, psychosocial, and economic aspects) and its impact on the patient’s family.

Angina pectoris is a clinical syndrome reflecting inadequate oxygen supply for myocardial metabolic demands with resultant ischemia. Depending upon the underlying pathophysiology, the patient will present with stable or unstable angina. The goals of therapy in elderly patients with angina (ischemic syndromes) are to (1) relieve the acute symptoms and stabilize the acute pathophysiological process; (2) minimize the frequency and severity of recurrent anginal attacks; and (3) prevent progression, plus cause regression of the underlying pathophysiological process. Therapeutic measures are directed at modifying the underlying pathophysiology with therapeutic agents and reducing myocardial ischemia by (1) reducing myocardial oxygen demand and (2) increasing coronary blood flow.

The main underlying pathological process in patients with angina is coronary atherosclerosis with plaque formation and narrowing of the vessel luminal diameter plus intermittent rupture of the atherosclerotic plaque. Because thrombus formation is an important factor in the progression of atherosclerotic lesions and in the conversion of clinical to acute events after plaque rupture, antiplatelet and anticoagulant therapy is important in the management of elderly CAD patients. In addition, stabilization and regression of the atherosclerotic lesions are possible by vigorous control of the patient’s serum lipids, particularly with hydroxymethylglutaryl coenzyme A (HMG CoA)-reductase inhibitors (statins), and treatment of other risk factors such as systemic hypertension, smoking, and diabetes mellitus.

The main determinants of myocardial oxygen demand are heart rate, myocardial contractility, and intramyocardial tension, which is a function of systemic pressure and ventricular volume. Reduction of the myocardial oxygen demand includes correction of potentially reversible factors such as heart failure, hyperthyroidism, valvular heart disorders (particularly aortic stenosis), obesity, emotional stress, hypertension, and arrhythmias such as atrial fibrillation. Drug therapy to reduce myocardial oxygen demand
Angina in the Elderly

is directed at reducing myocardial contractility, slowing heart rate, and limiting myocardial tension by reducing systemic pressure (afterload) and preload.

Coronary blood flow is dependent upon the duration of cardiac diastole, coronary arterial resistance, aortic diastolic pressure, and the availability of coronary collateral vessels. Improvement in coronary blood flow can be accomplished by these drugs, which increase the duration of diastole, decrease coronary artery resistance by vasodilatation by reducing intramyocardial tension, and stimulate the development of and flow through collateral vessels.

SPECIFIC DRUG THERAPIES

The principles of drug therapy for treating angina in elderly patients are the same as those for younger patients (13). The physician treating elderly patients, however, must be aware that the pharmacokinetics of drugs may be different in this age group. Gastrointestinal disorders may potentially interfere with drug absorption, although drug bioavailability is usually unaffected by the aging process (14). The decrease in lean body mass and the increase in adipose tissue associated with aging affect the volume of drug distribution. Hepatic blood flow and hepatic oxidation (phase I reactions) decrease with aging, whereas hepatic conjugation is unchanged. Not only is renal dysfunction common in elderly patients, but a 30% decline in glomerular filtration rate between the fifth and ninth decades in normal patients is also associated with aging (14). The elderly often demonstrate increased sensitivity to drugs of any given dosage and may tolerate side effects less well. The presence of comorbid conditions increases the potential for adverse drug reactions. The axiom to remember when prescribing drugs in elderly patients is to start low and titrate up slowly.

Given the pharmacological considerations of drug therapy in elderly patients, the specific antianginal drugs can be very effective in controlling symptoms and modifying the underlying pathophysiological process in elderly patients with angina. The classes of drugs commonly used include (1) nitrates, (2) β-blockers, (3) calcium channel blockers, and (4) antiplatelet and/or anticoagulant agents.

Nitrates

Nitrates are safe, effective, and usually the first choice for treatment of angina. Denitration of the organic nitrate with the subsequent liberation of nitric oxide (NO) is necessary for the drug to have therapeutic effects. NO stimulates guanylyl cyclase, which leads to the conversion of guanosine triphosphate to cyclic guanosine monophosphate, which causes relaxation of vascular smooth muscle with vasodilatation (15,16). The exact mechanism by which the organic nitrates undergo denitration and thus liberate NO remains controversial (17,18).

The active metabolite, NO, is also known as the endothelium-derived relaxing factor (EDRF) (19) which, in addition to relaxing vascular smooth muscle, reduces platelet adhesion and aggregation (20). In vessels with atherosclerosis, it has been shown that the endothelium is dysfunctional with attenuation of EDRF activity (21). Such attenuation of EDRF has been found in patients with hypercholesterolemia without overt coronary atherosclerosis (22). Because of this attenuated activity of EDRF, vascular vasoconstriction is predominant in patients with CAD. Therefore, nitrates as exogenous donors of NO would appear to be the ideal drug to use in elderly patients with angina (myocardial ischemia).
The mechanisms by which nitrates relieve and prevent myocardial ischemia include both (1) a reduction in myocardial oxygen demand and (2) an increase in myocardial oxygen supply due to the drug’s potent vasodilator properties (Table 1). Dilatation of capacitance veins reduces ventricular volume and preload, thus lowering myocardial oxygen requirement and improving subendocardial blood flow. Dilatation of systemic conductive arteries decreases afterload, another determinant of oxygen consumption. Nitrates dilate epicardial coronary arteries with an increase in coronary flow and an improvement in subendocardial perfusion. Nitrates also dilate collateral vessels, which can improve blood flow to the areas of ischemia (23). In the doses used clinically, nitrates do not affect coronary resistance vessels (24). Thus, the risk of myocardial ischemia due to coronary steal is minimal, which has been shown to occur with drugs such as dipyridamole and short-acting calcium channel blockers that cause arteriolar dilatation (25).

### Nitrate Preparations

**Short-acting nitrates.** Nitroglycerin is the drug most frequently used for relief from an acute anginal attack. It is given either as a sublingual tablet or as a sublingual spray and is absorbed rapidly with hemodynamic effects occurring within two minutes of drug administration. The advantage of the spray is that sublingual tablets deteriorate when exposed to light and will need to be renewed every four to six months to ensure complete bioavailability. The other advantage of nitroglycerin spray is that it may be easier to administer in elderly patients who have difficulty with the fine motor skills necessary to administer sublingual tablets. An inhalational form of nitroglycerin has just been approved for the management of acute anginal attacks. Oral nitrates are also available to abort acute anginal attacks that are not relieved with sublingual tablets or spray, and to prevent recurrent anginal attacks. Table 2 lists the different nitrate preparations and dosages (26).

**Long-acting nitrates.** Nitrates have been proven not only effective in relieving acute anginal pain, but also beneficial in preventing recurrent anginal attacks. Long-acting nitrates also improve exercise time until the onset of angina and reduce exercise-induced ischemic ST-segment depression (27,28). The oral preparation is usually the nitrate of choice in the prevention of angina. Standard-formulation isosorbide dinitrate is rapidly absorbed and is typically administered thrice a day with a 14-hour nitrate-free interval. Sustained-release isosorbide dinitrate has a slower rate of absorption and results in a therapeutic plasma concentration for 12 hours. The usual dosage schedule is twice daily in doses of 20 to 80 mg.

An isosorbide mononitrate is also available for the prevention of angina. The major advantage of the mononitrate preparation is that it is completely bioavailable because it does not undergo first-pass hepatic metabolism. To avoid drug tolerance, it is recommended...
that the 20- to 40-mg tablets be given twice daily with a seven-hour interval between doses. Also available is a sustained-release formulation of isosorbide mononitrate that provides therapeutic plasma drug concentrations for up to 12 hours each day and low concentrations during the latter part of the 24-hour period. The drug dose range is 30 to 240 mg given once daily.

Transdermal nitroglycerin is a topical nitroglycerin preparation that is effective in preventing angina, and may be particularly beneficial in elderly patients who take numerous pills and have difficulty in remembering drug schedules. Moreover, transdermal nitrate preparations will be more effective than oral preparations in elderly patients who have problems with gastrointestinal malabsorption. Transdermal nitroglycerin is available as an ointment or patch preparation. Both preparations are effective, although the patch obviates some of the inherent messiness of the ointment. As with the oral preparation, a 12- to 14-hour nitrate-free interval is necessary to avoid tolerance when using nitroglycerin ointment or patches.

Adverse Effects

Elderly patients, in general, tolerate nitrates without significant adverse effects, although the two major side effects, hypotension and headaches, can be extremely bothersome in certain patients. Hypotension may occur within minutes of sublingual administration of a nitrate or one to two hours after oral ingestion and is caused by the reduction in preload and afterload caused by the vasodilator effect of the drug. Symptoms may range from lightheadedness to syncope and are commonly positional and precipitated by standing. The hypotension related to nitrates more commonly occurs following the initial use of the drug, when hypovolemia is present, or with concomitant vasodilator therapy use such as calcium channel blockers or other antihypertensive drugs. The hypotension episode may also be potentiated by alcohol. The episodes can be alleviated by reducing the dose of nitrate, by correcting hypovolemia, and by avoiding an upright position after sublingual use of the drug. In certain elderly patients, the hypotension will be associated with bradycardia, which is similar to a typical vasovagal reaction. The hypotension associated with nitrate use will usually be alleviated by the patients lying down; in certain patients with a severe

### Table 2

<table>
<thead>
<tr>
<th>Medication</th>
<th>Usual dose (mg)</th>
<th>Onset of action (min)</th>
<th>Duration of action</th>
</tr>
</thead>
<tbody>
<tr>
<td>Short-acting</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sublingual nitroglycerin</td>
<td>0.3–0.6</td>
<td>2–5</td>
<td>10–30 min</td>
</tr>
<tr>
<td>Aerosol nitroglycerin</td>
<td>0.4</td>
<td>2–5</td>
<td>10–30 min</td>
</tr>
<tr>
<td>Sublingual and chewable isosorbide dinitrate</td>
<td>2.5–10</td>
<td>3–15</td>
<td>1–2 hr</td>
</tr>
<tr>
<td>Intravenous</td>
<td>5 µg/min to 30–80 µg/min</td>
<td>1</td>
<td>Sustained during infusion</td>
</tr>
<tr>
<td>Long-acting</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Oral isosorbide dinitrate</td>
<td>5–40</td>
<td>15–30</td>
<td>3–6 hr</td>
</tr>
<tr>
<td>Oral isosorbide dinitrate (SR)</td>
<td>40</td>
<td>30–60</td>
<td>6–10 hr</td>
</tr>
<tr>
<td>Oral erythritol tetrannitrate</td>
<td>10</td>
<td>30</td>
<td>Variable</td>
</tr>
<tr>
<td>Oral isosorbide mononitrate</td>
<td>5–60</td>
<td>30</td>
<td>6–8 hr</td>
</tr>
<tr>
<td>Transdermal nitroglycerin</td>
<td>5–15</td>
<td>30–60</td>
<td>8–14 hr</td>
</tr>
</tbody>
</table>

**Abbreviation:** SR, sustained release.

**Source:** From Ref. 26.
hypotensive reaction, elevation of the legs plus administration of fluid will be necessary.

The headache associated with nitrates can be a significant problem in certain elderly patients. It may be a mild, transient frontal headache, although in other patients the headache will be diffuse and throbbing, with persistent head and neck pain associated with nausea or vomiting. Such severe headaches are more common with the use of intravenous or transdermal nitrates. Nitrates may also aggravate vascular headaches and even initiate episodes of “cluster headaches.” As in the management of hypotension related to nitrates, the best approach to alleviate or prevent headaches is to use the lowest doses of nitrates possible and to titrate slowly upward if necessary. The use of an analgesic such as aspirin or acetaminophen in conjunction with the nitrate administration may prevent the associated headache. Commonly, because of vascular adaptation, within 7 to 10 days after initiation of nitrate use, the headache will diminish and subside. However, while waiting for adaptation to occur, elderly patients will require much reassurance to continue using the drug; and in certain elderly patients, a different antianginal drug will have to be substituted for the nitrate because the patient will not be able to tolerate the recurrent headaches.

Nitrate tolerance, defined as the loss of hemodynamic and antianginal effects during sustained therapy (29), is another consideration when treating elderly CAD patients. Tolerance has been shown to occur, regardless of the nitrate preparation, if the patient is continuously exposed to nitrates throughout a 24-hour period. The clinical impact of nitrate tolerance, however, is unknown, and the mechanism of nitrate tolerance remains unclear (29,30). Various possible hypotheses include (1) increased intravascular blood volume; (2) depletion of sulphydryl groups, which are needed for conversion of nitrates to NO; (3) activation of vasoconstriction hormones; and (4) an increased free-radical production by the endothelium during nitrate therapy (31–33). To prevent tolerance, it is recommended that a 12- to 14-hour nitrate-free interval be established when using long-acting nitrate preparations. During the nitrate-free interval, the use of another antianginal drug will be necessary. In elderly patients with unstable angina who receive continuous intravenous nitrates, tolerance is not a consideration; if tolerance develops in this setting, the dose of the nitrate should be increased.

Studies have demonstrated that abrupt withdrawal of nitrate exposure may produce nonatherosclerotic ischemic cardiac events, including myocardial infarction (MI) (34,35). Such events are presumably due to coronary artery spasm. Therefore, caution should be exercised when high-dose nitrate therapy is discontinued in elderly patients; if possible, the nitrate dose should be slowly tapered downward before discontinuation. Phosphodiesterase inhibitors such as sildenafil, vardenafil, and tadalafil used in the treatment of erectile dysfunction can be safely prescribed to patients with CAD but should not be used in patients receiving long-acting nitrates (36).

**β-Adrenergic Blockers**

β-Adrenergic blocking agents are effective in preventing angina and are considered by many authorities to be the drug of choice to prevent ischemic events. β-blockers also improve exercise time until the onset of angina and reduce exercise-induced ischemic ST-segment depression (37). β-blockers prevent angina mainly by causing a reduction in myocardial oxygen demand related to slowing of the heart rate, by depressing myocardial contractility, and by reducing blood pressure (Table 3). These effects are particularly impressive in the setting of increased emotional and physical stress, such as during exercise and high anxiety states. In addition to the reduction of myocardial oxygen
demand, β-blockers increase myocardial oxygen supply by slowing the heart rate and extending the period of diastole.

β-Adrenergic blocking agents can be classified according to (1) cardioselectivity, (2) intrinsic sympathomimetic activity, and (3) lipophilic activity (Table 4). Consideration of these specific properties is important when using the drug in elderly CAD patients. Cardioselectivity is determined by the extent the agent is capable of blocking β₁ receptors and not β₂ receptors (38). Certain agents such as metoprolol and atenolol are relatively more cardioselective than propranolol, which makes these drugs less prone to inducing bronchospasm or peripheral arterial vasoconstriction, as compared with the nonselective agents. At higher doses, however, cardioselective β-blockers react like nonselective agents with full potential for bronchospasm and peripheral arterial constriction.

Some β-blockers such as pindolol and acebutolol in addition to blocking β-adrenergic receptors, possess partial agonist properties and, therefore, are capable of producing intrinsic sympathetic stimulation (ISA) (39). The degree to which sympathomimetic activity is clinically apparent depends on the underlying sympathetic activity of the patient receiving the drugs. β-blockers with ISA may prevent slowing of the heart rate, depression of atrioventricular conduction, and a decrease in myocardial contractility in the setting of a low sympathetic state, such as when the patient is resting. When the sympathetic state is high, however, the effect of β-blockers with ISA is similar to that of the usual β-blockers, with a slowing of the heart rate and a decrease in blood pressure and ventricular

### Table 3  Cardiovascular Effects of β-Blockers and Mechanisms to Relieve Angina (Ischemia)

<table>
<thead>
<tr>
<th>Effect</th>
<th>Mechanism</th>
</tr>
</thead>
<tbody>
<tr>
<td>Decrease myocardial O₂ demand</td>
<td></td>
</tr>
<tr>
<td>Decrease contractility → ↓ blood pressure</td>
<td></td>
</tr>
<tr>
<td>Decrease heart rate → ↓ blood pressure and</td>
<td></td>
</tr>
<tr>
<td>Decrease myocardial blood flow (O₂)</td>
<td></td>
</tr>
<tr>
<td>Decrease heart rate → ↑ diastolic perfusion time</td>
<td></td>
</tr>
</tbody>
</table>

**Abbreviation:** CO, cardiac output.

### Table 4  Pharmacology of β-Blockers and Dosage

<table>
<thead>
<tr>
<th>Generic drug (brand)</th>
<th>Cardioselectivity</th>
<th>ISA</th>
<th>Lipophilic properties</th>
<th>Usual maintenance dose</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>(relative B₁ sensitivity)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Propranolol (Inderal)</td>
<td>0</td>
<td>0</td>
<td>high</td>
<td>10–40 mg, q.i.d.</td>
</tr>
<tr>
<td>Propranolol LA (Inderal LA)</td>
<td>0</td>
<td>0</td>
<td>high</td>
<td>40–240 mg, q.d.</td>
</tr>
<tr>
<td>Atenolol (Tenormin)</td>
<td>+</td>
<td>0</td>
<td>low</td>
<td>25–100 mg, q.d.</td>
</tr>
<tr>
<td>Metoprolol (Lopressor)</td>
<td>+</td>
<td>0</td>
<td>moderate</td>
<td>25–100 mg, b.i.d.</td>
</tr>
<tr>
<td>Metoprolol ER (Toprol XL)</td>
<td>+</td>
<td>0</td>
<td>moderate</td>
<td>50–200 mg, q.d.</td>
</tr>
<tr>
<td>Timolol (Blocadren)</td>
<td>0</td>
<td>0</td>
<td>low</td>
<td>10–20 mg, b.i.d.</td>
</tr>
<tr>
<td>Carvedilol</td>
<td>+</td>
<td>0</td>
<td>low</td>
<td>25 mg, b.i.d.</td>
</tr>
<tr>
<td>Acebutolol (Sectral)</td>
<td>+</td>
<td>+</td>
<td>low</td>
<td>200–600 mg, b.i.d.</td>
</tr>
<tr>
<td>Pindolol (Visken)</td>
<td>0</td>
<td>+</td>
<td>moderate</td>
<td>5–2 mg, t.i.d.</td>
</tr>
<tr>
<td>Labetalol (Normadyne)</td>
<td>0</td>
<td>0</td>
<td>low</td>
<td>100–600 mg, b.i.d.</td>
</tr>
<tr>
<td>Nadolol (Cogard)</td>
<td>0</td>
<td>0</td>
<td>low</td>
<td>40–80 mg, q.d.</td>
</tr>
<tr>
<td>Esmolol (Brevibloc injection)</td>
<td>+</td>
<td>0</td>
<td>low</td>
<td>0.10-0.15 μg/kg/min</td>
</tr>
</tbody>
</table>

**Abbreviations:** ER, extended release; LA, long-acting; ISA, intrinsic sympathomimetic activity.
contractility. It should be emphasized that β-blockers with ISA do not prevent sudden death in post-MI patients, as has been demonstrated with the use of the usual β-blockers; therefore, these agents are not recommended in elderly patients who have had an MI (40).

The various β-blockers differ with regard to their lipophilic properties. Some β-blockers such as propranolol and metoprolol are highly lipophilic, which facilitates transfer of the drug across the blood-brain barrier and, therefore, the lipophilic agents are more likely to produce central nervous system side effects, including mood changes, depression, and sleeping disturbances (41). In contrast, the hydrophilic β-blockers such as atenolol and nadolol are less likely to produce central nervous system side effects.

In general, β-blockers are well tolerated in elderly patients, and some studies have not shown any difference in the prevalence of drug side effects between older and younger patients (42). However, significant drug side effects may occur in elderly patients and may be life threatening. Bradycardia, secondary to the drug effects on the sinus node and atroventricular conduction, may occur and because of the attenuation of bronchodilation, asthmatic attacks may be precipitated by the drugs. Therefore, β-blockers are contraindicated in patients with significant bradycardia, unless a pacemaker is inserted, and in persons with a history of bronchospasm. The drugs should also be avoided, or used with caution, in persons with hypotension, hypoglycemic reactions, severe peripheral vascular disease with gangrene, mental depression, and severe heart failure secondary to severe LV systolic dysfunction. The possibility of a withdrawal rebound phenomenon with the activation of acute ischemic events should be considered when discontinuing β-blockers in elderly patients. Accordingly, if possible, the dose of β-blockers should be slowly tapered downward before discontinuation while another antianginal drug should be started; in addition, the patient should be advised to avoid strenuous activities during the tapering period.

β-blockers do have effects on serum lipids, which need to be considered when managing elderly CAD patients. Some studies have shown β-blockers to increase triglycerides and to decrease HDL cholesterol, although no significant change was noted in total cholesterol or LDL cholesterol (43). Other studies have not demonstrated a significant effect of long-term propranolol use in serum lipids in elderly persons (44). Patients with angina pectoris should be treated with β-blockers (45,46).

**Calcium Channel Blockers**

Calcium channel blockers are usually not considered as first-line drugs in elderly patients with acute coronary artery syndromes. Unlike β-blockers, their effects are less predictable and they have not been shown to reduce mortality, sudden death, or reinfarction in post-MI patients. The studies that have shown increase in morbidity and mortality with the use of these drugs in treating hypertension or CAD are also disturbing (47,48). In turn, calcium blockers have cardiovascular effects that can be beneficial in preventing and controlling angina. In general, calcium blockers exert their effect by inhibiting influx of calcium ions through calcium channels of cardiac and vascular smooth muscle cells. Because of this inhibition of calcium influx, myocardial contractility is decreased, dilatation of the peripheral and coronary vasculature occurs, and sinus node and atroventricular conduction functions are suppressed. Therefore, myocardial oxygen demand is reduced by the decrease in preload and afterload and the decrease in myocardial contractility. Slowing of the heart rate, which occurs with the use of non-dihydropyridine calcium blockers such as verapamil and diltiazem is also effective in decreasing myocardial oxygen demand. In addition to reducing the myocardial oxygen demand, calcium blockers can improve the myocardial oxygen supply by relaxing the
tone of coronary arteries and by promoting the development of coronary collaterals (Table 5). This property of relaxing coronary vasculature tone is particularly beneficial when Prinzmetal’s angina (vasospasm) is present.

Calcium channel blockers are usually divided into the dihydropyridine and non-dihydropyridine groups (Table 6). Nifedipine was the first dihydropyridine made available for the treatment of angina, but newer generations of dihydropyridine agents are now available, including nicardipine, nisoldipine, nimodipine, felodipine, amlodipine, and isradipine. Nifedipine is a potent coronary and peripheral artery vasodilator with negative inotropic properties. Significant afterload reduction occurs due to the vasodilation. At therapeutic doses, nifedipine has only a minor effect on the sinus and atrioventricular nodes; thus because of the decrease in afterload, sympathetic reflex increases in heart rate commonly occur when the drug is administered. The increased heart rate may ameliorate the negative inotropic effect, and clinically hemodynamic indices of contractility are generally unaffected. Because of intense vasodilation of the peripheral coronary circulation, however, the possibility of a coronary steal phenomenon has to be considered when using the drug (49). Such a phenomenon is more common when using a short-acting drug preparation and in patients with severe three-vessel CAD. Therefore, a β-blocker should be added if nifedipine is used to treat elderly patients with acute ischemic syndromes. A sustained-release preparation of nifedipine is now available, which results in less sympathetic activity and is

Table 5  Cardiovascular Effects of Calcium Blockers and Mechanisms to Relieve Angina

<table>
<thead>
<tr>
<th>Effect</th>
<th>Mechanism</th>
</tr>
</thead>
<tbody>
<tr>
<td>Decreased myocardial O2 demand</td>
<td>Arteriolar vasodilatation ↘ afterload ↘ wall tension</td>
</tr>
<tr>
<td>Decrease contractility</td>
<td>Decrease heart rate</td>
</tr>
<tr>
<td>Increase myocardial blood flow</td>
<td>Decrease heart rate ↗ diastolic perfusion time</td>
</tr>
<tr>
<td>Coronary vasodilatation</td>
<td>Coronary vasodilatation ↗ flow</td>
</tr>
</tbody>
</table>

Table 6  Calcium Channel Blocker Preparations and Dosage

<table>
<thead>
<tr>
<th>Generic drug (brand)</th>
<th>Potential for SA node and AV node depression</th>
<th>Potential for depression of myocardial contractility</th>
<th>Usual adult oral dosage (mg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nifedipine (Procardia) (Adalat)</td>
<td>0</td>
<td>0 to +</td>
<td>10–30, t.i.d.</td>
</tr>
<tr>
<td>Nifedipine GITS (Procardia XL)</td>
<td>0</td>
<td>0 to +</td>
<td>30–90, q.d.</td>
</tr>
<tr>
<td>Nicardipine (Cardene)</td>
<td>0</td>
<td>0 to +</td>
<td>20–30, t.i.d.</td>
</tr>
<tr>
<td>Amlodipine (Norvasc)</td>
<td>0</td>
<td>0</td>
<td>2.5–10, q.d.</td>
</tr>
<tr>
<td>Felodipine (Plendil)</td>
<td>0</td>
<td>0</td>
<td>2.5–20, q.d.</td>
</tr>
<tr>
<td>Diltiazem (Cardizem)</td>
<td>++</td>
<td>+</td>
<td>30–90, t.i.d.</td>
</tr>
<tr>
<td>Diltiazem CD (Cardizem CD)</td>
<td>++</td>
<td>+</td>
<td>120–300, q.d.</td>
</tr>
<tr>
<td>Verapamil (Isoptin) (Calan)</td>
<td>++</td>
<td>++</td>
<td>40–120, t.i.d.</td>
</tr>
<tr>
<td>Verapamil SR (Isoptin SR) (Calan SR)</td>
<td>++</td>
<td>++</td>
<td>120–240, q.d.</td>
</tr>
</tbody>
</table>

Abbreviations: CD, extended release; GITS, gastrointestinal therapeutic system; SR, sustained release.

Source: From Ref. 26.
considered to be a safer agent than the shorter-acting preparations. Nevertheless, the addition of a β-blocker with nifedipine, regardless of the type of preparation, is considered the best approach when managing elderly patients with acute ischemic syndromes. The second-generation dihydropyridines such as amlodipine and felodipine have greater vascular selectivity and less negative inotropy and have no clinical effect on the sinus or atroventricular nodes. Therefore, coronary artery steal does not appear to be a major concern with these drugs, and the drugs can be used in elderly patients with LV systolic dysfunction.

Verapamil and diltiazem, two non-dihydropyridine agents, are both potent inhibitors of sinus node activity and atroventricular node conduction, in addition to being peripheral vasodilators (Table 6). Both drugs have significant negative inotropic effects. Because of these effects, the drugs are effective antianginal agents; however, caution is necessary when using the drugs in elderly patients with bradycardia and depressed LV systolic function. These drugs are contraindicated in patients with LV systolic dysfunction with or without clinical heart failure, in patients with disorders of the sinus node, and in patients with heart block. The Multicenter Diltiazem Postinfarction Trial reported an increased mortality in postinfarction patients with heart failure or abnormal LV ejection fraction who were randomized to diltiazem therapy (50). Therefore, if a calcium channel blocker is necessary to control angina in elderly postinfarction patients with depressed LV systolic function, second-generation dihydropyridines such as amlodipine and felodipine should be used instead of diltiazem or verapamil.

Extreme caution is required when using diltiazem or verapamil in combination with a β-blocker, particularly in elderly patients who demonstrate sinus node or atrioventricular conduction dysfunction, or in elderly patients who have depressed LV systolic function. Some authorities recommend ECG monitoring when initiating these drugs, particularly verapamil, in combination with β-blockers.

It should be emphasized that the American College of Cardiology/American Heart Association (ACC/AHA) guidelines state that there are no Class I indications for using calcium channel blockers during or after MI (51). However, if angina pectoris persists despite the use of β-blockers and nitrates, long-acting calcium channel blockers such as dilatiazem or verapamil should be used as antianginal agents in elderly patients with CAD and normal LV systolic function and amlodipine or felodipine in patients with CAD and abnormal LV systolic function.

**Aspirin**

Recent knowledge of the importance of thrombus formation in acute coronary syndromes and the results of studies demonstrate a decreased incidence of MI in patients taking daily aspirin compared with patients receiving placebo (52). The updated ACC/AHA guidelines for the management of patients with stable angina pectoris (45) and the American College of Physicians clinical practice guidelines (46) recommend treating all patients with CAD with aspirin in a dose of 75 to 325 mg daily unless there are contraindications to the use of this drug. The use of enteric low dose aspirin may be associated with aspirin resistance (a lack of an antiplatelet effect) and a 160-mg aspirin dose may need to be prescribed.

In an observational prospective study of 1410 patients, mean age 81 years, with prior MI and hypercholesterolemia, 59% of patients were treated with aspirin (50) and at 36-month follow-up, the use of aspirin was associated with a 52% reduction in new coronary events (53).
Angina in the Elderly

Ticlopidine and Clopidogrel

Not all patients can tolerate aspirin, and recently an aspirin-resistance phenomenon has been described in patients where there is little-to-no antiplatelet effect from the drug. Ticlopidine and clopidogrel are useful alternatives to aspirin when the drug is not tolerated, although these have their own associated toxicities (54). This toxicity may, however, be dose related in most situations.

Clopidogrel in a dose of 75 mg daily is recommended in patients who cannot tolerate aspirin (45,46,52,55). Dipyridamole should not be used in patients with angina pectoris since it can cause a coronary steal syndrome and increase exercise-induced myocardial ischemia (56).

Other Adjunctive Treatments

Angiotensin-Converting Enzyme Inhibitors and Angiotensin Receptor Blockers

On the basis of the results of various clinical trials, there is now strong evidence that angiotensin-converting enzyme (ACE) inhibitors can reduce the frequency of new cardiovascular events in both normotensive and hypertensive patients with known vascular disease and in patients with diabetes mellitus. If tolerated, ACE inhibitors should be part of a medical regimen to treat chronic ischemic heart disease (57). Angiotensin I receptor blockers are now being studied in patients with known ischemic heart disease who have no history of a previous MI or LV dysfunction.

Statins

Numerous studies have demonstrated that statins reduce cardiovascular morbidity and mortality in elderly patients with CAD including those with stable angina pectoris (58–65). The low-density lipoprotein cholesterol should be reduced to less than 70 mg/dL in patients with stable angina pectoris (63,64). The updated ACC/AHA guidelines for management of patients with chronic stable angina pectoris (45) and the ACP clinical practice guidelines (46) both recommend treating patients with chronic stable angina pectoris with lipid-lowering drug therapy.

AN APPROACH TO MANAGEMENT:
SPECIFIC PRACTICE CONSIDERATIONS

Unstable Angina

Unstable angina is a transitory syndrome that results from disruption of a coronary atherosclerotic plaque with the subsequent cascade of pathological processes, including thrombosis formation that critically decreases coronary blood flow resulting in new onset or exacerbation of angina (ischemia) (66). Transient episodes of vessel occlusion or near occlusion by thrombus at the site of plaque injury may occur and lead to angina at rest. The thrombus may be labile and result in temporary obstruction to flow. Release of vasoconstrictive substances by platelets and vasoconstriction secondary to endothelial vasodilator dysfunction can contribute to further reduction in blood flow (67), and in some patients myocardial necrosis (non-Q-wave infarction) is documented. Table 7 lists the various clinical presentations that are classified as unstable angina.

In contrast to elderly patients with stable angina who do not require hospitalization, elderly patients with unstable angina are usually hospitalized and, depending upon their risk stratification, may require monitoring in an intensive care unit. Severe classification
schemes of risk stratification have been developed. Table 8 lists a classification that subdivides patients into high-, intermediate-, and low-risk groups (68). As noted by this classification, clinical characteristics are readily identifiable on the initial patient evaluation that stratifies the patient into low-, intermediate-, or high-risk subgroups for hospital complications. For example, acute resting ischemic ECG abnormalities markedly worsen the prognosis. Other characteristics that identify the high-risk patient include prolonged ongoing rest pain longer than 20 minutes and signs of LV dysfunction (S3, rales, new murmur or mitral regurgitation). Within each subgroup of unstable angina, it is important to recognize certain elderly patients who have specific characteristics that will influence therapy. Recurrent angina after PTCA is a common clinical event related to partial artery restenosis and occurs in as many as 40% of patients within the first three to six months post-PTCA, regardless of the patient’s age. The prognosis is favorable, and the elderly patient can usually be stabilized medically prior to a scheduled repeat angiogram and a possible repeat PTCA. Angina after intracoronary stent placement occurs less frequently than after an isolated angioplasty and is often the result of subacute closure due to thrombus formation. These patients are at higher risk for MI and are usually managed as higher-risk patients (69). Patients with angina following CABG are another subgroup of elderly patients who require specific considerations. Since the risk of reoperation is higher than that of the initial surgery, surgeons are often reluctant to reoperate in elderly patients, especially on those elderly patients who have undergone internal mammary grafting. Medical therapy is usually the first approach to this subgroup of elderly patients with unstable angina. Other clinical subgroups of elderly patients with unstable angina who require special considerations are the patient with a non-Q-wave infarction, variant angina, and cocaine intoxication.

Table 9 lists the ACC/AHA stratification of patients with unstable angina into high-risk, intermediate-risk, and low-risk groups for short-term risk of death or nonfatal MI.
Angina in the Elderly

Table 9 Risk Stratification of Patients With Unstable Angina for Short-Term Risk of Death or Nonfatal MI

<table>
<thead>
<tr>
<th>High Risk (at least one of following factors)</th>
<th>Intermediate risk (no high-risk feature but one of the following features)</th>
<th>Low risk (no high- or intermediate-risk feature)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Accelerating tempo of ischemic symptoms in prior 48 hr</td>
<td>Prior MI or CABG; peripheral or cerebrovascular disease; prior aspirin use</td>
<td>—</td>
</tr>
<tr>
<td>Prolonged ongoing (&gt;20 min) rest pain</td>
<td>Prolonged (&gt;20 min) rest angina, now resolved, with moderate or high likelihood of CAD; rest angina (&lt;20 min or relieved with rest or sublingual NTG)</td>
<td>New-onset CCS Class III or IV angina in past 2 wk with moderate or high likelihood of CAD</td>
</tr>
<tr>
<td>Pulmonary edema; new or worsening MR murmur; $S_1$ or new/worsening rales; hypotension, tachycardia, bradycardia; age &gt;75 yr</td>
<td>Age &gt;70 yr</td>
<td>—</td>
</tr>
<tr>
<td>Angina at rest with transient ST-segment changes &gt;0.05 mV; bundle branch block, new or presumed new; sustained ventricular tachycardia</td>
<td>T-wave inversions &gt;0.2 mV; pathological Q-waves</td>
<td>Normal or unchanged ECG during episode of chest discomfort</td>
</tr>
<tr>
<td>Markedly elevated troponin T or I (&gt;0.1 ng/mL)</td>
<td>Slightly elevated troponin T or I (&gt;0.01 but &lt;0.1 ng/mL)</td>
<td>Normal</td>
</tr>
</tbody>
</table>

Abbreviations: MI, myocardial infarction; CABG, coronary artery bypass graft surgery; CAD, coronary artery disease; CCS, Canadian Cardiovascular Society; NTG, nitroglycerin; MR, mitral regurgitation.

Source: Adapted from Ref. 70.

Following risk stratification of the elderly patient with unstable angina, therapy should be initiated. The initial goals of therapy should be to alleviate symptoms by decreasing myocardial oxygen demand and increasing myocardial blood flow and to stabilize the atherosclerotic plaque. Furthermore, a plan to promote regression of the atherosclerotic lesion should be initiated during the patient’s hospitalization.

Therapy, including drug therapy, should be started in the emergency department; it should not be delayed until hospital admission. Reversible factors causing angina should be identified and corrected. These include anemia, which may require packed red cell transfusion. Electrocardiographic monitoring is important since arrhythmias can occur and ST-T changes are a marker for an increased risk of complications. The aggressiveness of the drug dosage will depend upon the severity of symptoms and will need modification through the elderly patient’s hospitalization. Oxygen should be given to patients with cyanosis, respiratory distress, heart failure, or high-risk factors. Oxygen therapy should be guided by arterial saturation; its use when the baseline saturation is more than 94% is questionable. Morphine sulfate should be administered intravenously when symptoms are not immediately relieved with nitroglycerin or when acute pulmonary congestion and/or severe agitation is present.

Aspirin should be given to all patients with unstable angina unless contraindicated and continued indefinitely. Clopidogrel should be administered to patients who are unable
to tolerate aspirin because of hypersensitivity or major gastrointestinal intolerance. Data from the Clopidogrel in Unstable Angina to Prevent Recurrent Events (CURE) trial favor the use of aspirin plus Clopidogrel for nine months in patients with unstable angina (71). The ACC/AHA guidelines for unstable angina support the use of aspirin plus clopidogrel in high-risk and intermediate-risk patients with unstable angina, with clopidogrel withheld for five to seven days if CABG is planned (72).

Parenteral anticoagulation with intravenous infractionated heparin or preferably with subcutaneous low-molecular-weight heparin (73–76) should be added to antiplatelet therapy in patients with high-risk or intermediate-risk unstable angina. The revised ACC/AHA guidelines for unstable angina also recommend adding a platelet glycoprotein IIb/IIIa inhibitor in addition to aspirin, clopidogrel, and low-molecular–weight heparin in patients with continuing ischemia or with other high-risk features, and to patients in whom PTCA is planned. Eptifibatide and tirofiban are approved for this use (70). Abciximab can also be used for 12 to 24 hours in patients with unstable angina in whom PTCA is planned within the next 24 hours (70).

As with the use of aspirin, nitrates should be instituted quickly in the emergency department. Patients whose symptoms are not fully relieved with three sublingual nitroglycerin tablets should receive continuous intravenous nitroglycerin. The initial dose is 5 to 10 mg/min, and the dose should be titrated every three to five minutes to relieve symptoms of associated hypertension. If angina is relieved, then an oral or transdermal preparation can be started after 24 hours of intravenous therapy. β-blockers (in addition to aspirin, heparin, and nitrates) should also be started in the emergency room unless there are contraindications. Intravenous loading (e.g., metoprolol 5 mg for 5 minutes, repeated every 15 minutes for a total of 15 mg) or propranolol followed by oral therapy is recommended. A continuous β-blocker intravenous infusion may be used (esmolol, starting maintenance dose of 0.1 g/kg/min intravenously with upward titration in increments of 0.5 g/kg/min every 10 to 15 minutes as tolerated by blood pressure until the desired response has been obtained, limiting symptoms develop, or a dose of 0.20 mg/min is reached). An oral ACE inhibitor and a statins drug should also be administered unless there are contraindications.

Interventional Therapy

The majority of elderly patients with stable and unstable angina can be stabilized with medical management. Patients who continue to have unstable angina 30 minutes after initiation of therapy or who have recurrent unstable angina during the hospitalization are at increased risk for MI or cardiac death. In addition, patients who demonstrate major ischemic complications, such as pulmonary edema, ventricular arrhythmias, or cardiogenic shock associated with unstable angina also have a poor prognosis. In these patients, emergency cardiac catheterization should be performed with the consideration of interventional therapy (CABG or PTCA). Insertion of an intra-aortic balloon pump may be necessary in some of these elderly patients.

For the majority of elderly patients whose angina is stabilized, two alternate strategies for definitive treatment of angina need to be considered: “early invasive” and “early conservative” (77). The “early invasive strategy” approach is to perform cardiac catheterization in all patients after 48 hours of presentation unless interventional therapy is contraindicated because of extensive comorbidities. In contrast, the “early conservative” strategy is to perform cardiac catheterization only in patients who have one or more of the following high-risk indicators: prior revascularization, associated congestive heart failure or depressed LV ejection fraction (<50%) by noninvasive study, malignant
ventricular arrhythmia, persistent or recurrent pain/ischemia, and/or a functional study (stress test) indicating high risk. On the basis of data from the Treat Angina with Aggrastat and determine Cost of Therapy with an Invasive or Conservative Strategy (TACTICS)—Thrombolysis in Myocardial Infarction 18 study, an early invasive strategy is superior to a conservative strategy in high-risk unstable angina patients (78). The revised ACC/AHA guidelines recommend an early invasive strategy for all high-risk patients with unstable angina.

A stress test can be performed 48 to 72 hours after the patient has stabilized. The choice of the type of stress testing (exercise, exercise with imaging, or pharmacological) will depend upon the resting ECG findings and the patient’s ability to exercise.

Myocardial revascularization is indicated in (1) patients who, at catheterization, are found to have significant left main CAD (≥50%) or a significant (≥70%) three-vessel disease with depressed LV function (LV ejection fraction <50%); (2) patients with two-vessel disease with proximal severe subtotal stenosis (≥95%) of the left anterior descending coronary artery and depressed LV ejection fraction; and (3) patients with significant CAD if they fail to stabilize with medical treatment, have recurrent angina/ischemia at rest or with low-level activities, and/or if ischemia is accompanied by congestive heart failure symptoms, an S3 gallop, new or worsening mitral regurgitation, or definite ECG changes (77).

The ACC/AHA guidelines recommend CABG for patients with unstable angina with significant left main CAD, three-vessel CAD, and for two-vessel CAD with significant proximal left anterior descending CAD and either abnormal LV function (LV ejection fraction <50%) or demonstrable ischemia on noninvasive testing (70). PTCA or CABG is recommended for patients with one-vessel or two-vessel CAD without significant proximal left anterior descending CAD, but with a large area of viable myocardium and high-risk criteria on noninvasive testing. PTCA is recommended for patients with multivessel CAD with a suitable coronary anatomy with normal LV function and without diabetes mellitus (70).

For some patients without these high-risk features, revascularization may still be an option, depending on recurrent symptoms, test results, and patient preferences. The healthcare team should educate patients and their families or advocate about the expected risks and benefits of revascularization and determine individual patient preferences and fears that may affect the selection of therapy. CABG, with or without cardiopulmonary bypass, causes a high incidence of cognitive decline (79).

Interventional therapy with PTCA, atherectomy, and/or some combination of PTCA and coronary artery stenting has increased in usage in patients with CAD, diminishing the frequency of CABG. Studies comparing PTCA and CABG have been performed, and, generally, the results of PTCA and CABG are similar in reference to mortality. However, an increased incidence of recurrent angina and need for revascularization procedure occurs with PTCA (80–82). On the other hand, the incidence of cognitive decline is high in older persons undergoing CABG with no difference seen when comparing the incidence of cognitive dysfunction in on-pump and off-pump bypass procedures (79). Further studies are necessary to determine if coronary stenting in conjunction with PTCA will decrease the incidence of recurrent angina and the need for revascularization.

Stable Angina

Elderly patients with stable angina who are at “low risk” (preserved LV function and no left main CAD) can be treated as effectively with medical therapy as with interventional therapy. In patients with stable angina, the atherosclerotic lesions are predominantly
advanced fibrolipoid plaques or fibrotic lesions (83). Usually no plaque ulceration or thrombosis is present, and the main cause of angina is the reduction of luminal diameter of the coronary vessel due to chronic atherosclerosis. Therefore, therapy is directed at decreasing myocardial oxygen demand and increasing coronary blood flow. In addition, prevention of plaque instability and initiation of therapy to cause regression of the atherosclerotic lesion are necessary.

Studies have not demonstrated any significant benefit of a specific class of antianginal drugs compared with other classes in treatment of stable angina. Therefore, the choice of a single antianginal drug will depend upon the clinical situation, contraindications, and the physician’s preference. Surely, a β-blocker should be the first choice in elderly patients who have a history of MI or demonstrate electrocardiographic evidence of silent infarction or silent myocardial ischemia (84).

Combination drug therapy, in which a β-blocker and a vasodilator are used, is highly advantageous in treating elderly patients with angina. Studies have shown that combination therapy with a nitrate and a β-blocker decreases the number of anginal attacks and increases the duration of treadmill stress testing as compared with either nitrates or β-blockers alone (85). The combination of a β-blocker and a calcium channel blocker has also been shown to be more effective in reducing angina and extending exercise time than monotherapy (85). Such a combination can be very beneficial when attempting to control both hypertension and angina in elderly patients. In turn, caution is necessary when using β-blockers in combination with diltiazem or verapamil because of the potential risk of provoking serious bradycardia or precipitating heart failure. This therapy is particularly a concern when verapamil and a β-blocker are used in combination, and when underlying sinus or atrioventricular nodal disease or LV systolic dysfunction is present. In elderly patients whose angina is refractory to double drug therapy, triple drug therapy may be necessary. Such a therapy would include a β-blocker, a long-acting nitrate, and a calcium channel blocker. It may be beneficial in preventing anginal attacks. However, elderly patients taking these multiple drugs will need to be monitored closely for side effects, and the drugs should be started at low doses. Patients aged 75 years or older with angina, despite standard drug therapy, benefit more from coronary revascularization (86,87).

A preventive program in elderly patients with angina is mandatory, including abstinence from smoking, treatment of hypertension, use of aspirin and ACE inhibitors, an exercise program, and control of lipids and weight. Treatment of associated heart failure and anemia can also prevent or relieve symptoms of angina. The recent studies that have demonstrated the efficacy of statin therapy in lowering serum lipids and in preventing future coronary events in elderly patients with CAD (58–65) compel physicians to screen elderly anginal patients for elevated serum lipids and to be aggressive in their treatment of lipid abnormalities. In the Heart Protection Study, 20,536 adults up to age 80 years with CAD, other occlusive arterial disease, or diabetes mellitus were randomized to simvastatin 40 mg daily or double-blind placebo and followed for a mean of five years (62). All-cause mortality, coronary events, stroke, and coronary and noncoronary revascularization were significantly reduced by simvastatin, regardless of age and initial serum lipids (62).

In addition, elderly patients will require counseling in reference to lifestyle, with avoidance of activities that “trigger” ischemic attacks (88). The physician will need to be aware of the potential for the development of mental depression in elderly CAD patients. The symptoms of depression may be subtle in elderly patients and will progress unless the disease is treated. Depression has also been shown to be a risk factor for future coronary events in patients with CAD (89).
Angina in the Elderly

The role of exercise should be emphasized when managing elderly patients with angina. Exercise programs that progressively increase physical endurance and reduce the heart rate and cardiac work at any given level of activity lead to improvement in cardiac performance and prolong exercise time before onset of angina (90). In addition, some studies have shown stress-induced myocardial ischemia (as assessed by thallium 201 scintigraphy) to be significantly decreased after a one-year program of supervised exercise and low-cholesterol diet in patients with stable angina (91). Caution is necessary, however, when initiating an exercise program in elderly CAD patients. Elderly patients should be screened for high-risk characteristics, including results of a stress test, before starting an exercise program since exercise can provoke serious arrhythmias in high-risk patients, especially in poorly conditioned patients. Other exercise programs can be advised according to the patient’s needs and preference, such as swimming or stationary cycling.

New Approaches for the Management of Angina

Over the years, the management of patients with angina has changed, and new approaches have developed. Some of these changes are due to increased knowledge of the underlying pathophysiology of myocardial ischemia with the development of new drugs. Other changes are related to the development of innovative mechanical devices and techniques that theoretically should relieve angina.

Ranolazine

Ranolazine is a piperazine derivative and a partial fatty acid oxidation inhibitor that reduces calcium overload in the ischemic myocyte by inhibition of the late sodium current (92,93). This action decreases the magnitude of ischemia-induced sodium and calcium overload, improving myocardial function as well as myocardial perfusion. Four randomized, double-blind trials have demonstrated that ranolazine reduces frequency of angina episodes and nitroglycerin consumption and improves exercise duration and time to anginal attacks without clinically significant effects on heart rate or blood pressure (94–97).

Ranolazine was approved by the US Food and Drug Administration (FDA) for treatment of patients with chronic stable angina pectoris in January 2006. Ranolazine was approved for use as a combination therapy when angina is not adequately controlled with other antianginal drugs. The recommended dose of sustained-release ranolazine is 750 mg or 1000 mg twice daily.

Other Pharmacological Approaches

Other drugs under investigation and being considered for FDA approval include nicorandil and ivabradine. Nicorandil is a coronary vasodilator with a unique dual mechanism of action that involves a nitrare-like effect and a potassium ion channel opening action (92,98). The Impact of Nicorandil in Angina (IONA) study showed at 1.6-year follow-up in patients with stable angina pectoris that 2565 patients randomized to nicorandil 20 mg twice daily had a 17% significant reduction in CAD death, nonfatal MI, or unplanned hospital admission for cardiac chest pain compared with 2561 patients randomized to placebo (99).

Ivabradine is a heart rate lowering drug that acts specifically on the sinoatrial node (100). Ivabradine caused dose-dependent improvements in exercise tolerance and time to development of ischemia during exercise (101).
Cell Therapy

Innovative approaches for the management of drug resistant angina pectoris include the use of vascular growth factors to induce myocardial angiogenesis (102,103). Granulocyte macrophage colony stimulating factor has been used to mobilize bone marrow stem cells to induce angiogenesis. In addition, stem cells are being used by direct injection to affect new vascular growth (103).

Other Mechanical Approaches

Recent mechanical techniques for the treatment of angina include transmyocardial laser revascularization (TMLR), enhanced external counter pulsation (EECP), and spinal cord stimulation (SCS). These approaches have been used in patients with severe angina who are not candidates for PTCA or CABG, usually because of diffuse CAD or extreme comorbidities. Such approaches would appear to be suitable for many elderly CAD patients who may have inoperable CAD and multiple comorbidities plus angina that is difficult to control with medical therapy.

TMLR employs a high-energy laser beam to create channels in the myocardium from the epicardial to the endocardial surface (104). The channels allow oxygenated LV blood to perfuse ischemic myocardial zones (105). The human myocardium contains an extensive network of sinusoids, and TMLR, theoretically, delivers oxygenated blood to these sinusoids with improved myocardial oxygen delivery to the ischemic region. Data on the efficacy of TMLR in improving anginal symptoms and exercise capacity are controversial (106–108).

EECP is a noninvasive outpatient treatment designed to increase coronary flow in the treatment of angina (109). This treatment involves wrapping the calves, thighs, and buttocks with pneumatic cuffs. Synchronized pulsatory pressure is applied sequentially from calves to thighs during diastole, returning arterial blood to the heart to increase diastolic pressure in the coronary vessels. Pressure is relieved during systole, reducing afterload and cardiac work, thus decreasing myocardial oxygen demand. The typical course of treatment is 35 one-hour sessions over a period of seven weeks. EECP has been shown to improve ischemia in patients who have thallium reperfusion evidence of ischemia. In one study of patients who received EECP, 75% of subjects had resolution of ischemia, demonstrated by improved thallium scintigraphy with normal thallium stress tests, except for areas scarred by previous MIs (110). In addition, the subjects showed exercise improvement. A controlled study of 139 patients showed a reduction in anginal episodes, an increase in the time to 1-mm ischemic ST-segment depression, and a trend toward reduced nitroglycerin use in the EECP group but a similar increase in exercise duration in both groups (111).

SCS has been demonstrated to cause clinical improvement in patients with refractory angina pectoris in the number of anginal episodes, in nitroglycerin consumption, in maximal exercise time, in exercise time until angina, in the number of episodes of myocardial ischemia, in the duration of episodes of myocardial ischemia, and in ischemic ST-segment depression at a comparable workload (112,113). Double-blind, randomized, placebo-controlled studies have not been performed with SCS. The clinical improvement from SCS occurred despite no evidence of improvement in regional myocardial blood flow during exercise or in myocardial oxygen consumption as assessed by the heart rate times systolic pressure product at maximal exercise. The mechanisms of clinical improvement by SCS are unclear. SCS must be considered experimental at this time and is a therapeutic option for the treatment of refractory angina pectoris in patients unable to have coronary revascularization or at very high risk for coronary revascularization.
Angina in the Elderly

On the basis of the results of these preliminary studies, these new techniques may have a role in the management of certain elderly patients with angina. Further studies are necessary, however, before these new approaches can be recommended as therapy for the management of elderly patients with severe angina refractory as opposed to conventional medical therapy.

REFERENCES


Therapy of Acute Myocardial Infarction

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INTRODUCTION
In 2004, there were 732,000 hospital admissions in the United States with a first-listed diagnosis of acute myocardial infarction (MI) (1). Of these, 460,000 (62.8%) occurred in the 12.4% of the population aged 65 years or older, 42.3% occurred in the 6.1% of the population over the age of 75, and 17.1% occurred in the 1.6% of the population over the age of 85 (1). Moreover, approximately 85% of all deaths attributable to acute MI occur in patients over age 65, and 60% occur in patients over age 75 (1,2). Thus, acute MI is exceedingly common in older adults, and the case fatality rate is disproportionately high. This chapter reviews the treatment of elderly patients with acute MI, including the management of selected complications.

GUIDING PRINCIPLES
Numerous studies have demonstrated that elderly patients with acute MI are at increased risk for a variety of complications, including atrial fibrillation, congestive heart failure, myocardial rupture, cardiogenic shock, and death (3–9). The risk of each of these complications is two- to fourfold higher in patients over age 65 than in younger patients. Older age thus defines a high-risk subgroup of MI patients who could potentially derive substantial benefit from aggressive therapeutic interventions. On the other hand, elderly patients are at increased risk for serious adverse consequences arising from aggressive treatments such as fibrinolytic therapy or early catheterization and percutaneous coronary intervention (PCI). In addition, the risk–benefit ratio may be modulated by the presence of comorbid conditions (e.g., diabetes, renal insufficiency, dementia), and the desirability of specific therapies may be further affected by social considerations and patient preferences. Therefore, the potential benefits and risks of each intervention must be carefully considered on an individualized basis.

While elderly MI patients clearly represent a high-risk subgroup, it is important to recognize that they also comprise an extremely heterogeneous subgroup, and this heterogeneity has important therapeutic implications. For example, an 80-year-old patient...
presenting with a large anterior MI complicated by heart failure and hypotension has an expected mortality of over 50%. As a result, the potential benefit to be derived from maximally aggressive therapy (e.g., immediate catheterization and PCI) is large, thereby justifying a moderate increase in procedural risk. In contrast, an 80-year-old individual presenting with a small inferior MI of more than 12 hours’ duration who is hemodynamically stable and free of chest pain has a relatively favorable prognosis, and the risks associated with thrombolysis and PCI may not be justified. Thus, in considering the interventions described below, the clinician should keep in mind that the “sickest” patients often have the most to gain from aggressive treatment, while those with a more favorable prognosis often respond satisfactorily to conservative management.

GENERAL MEASURES

As in younger patients, the early management of older patients with acute MI should include measures designed to relieve the patient’s discomfort and treat any hemodynamic disturbances, such as heart failure or hypotension (Table 1). Morphine sulfate in doses of 2 to 4 mg intravenously is the recommended agent for treating chest pain in patients with

<p>| Table 1 | General Measures for the Early Management of Elderly Patients with Acute Myocardial Infarction |
| -- | -- | -- | -- |</p>
<table>
<thead>
<tr>
<th>Symptom or sign</th>
<th>Agent</th>
<th>Dose</th>
<th>Comment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chest pain</td>
<td>Oxygen</td>
<td>2–5 L/min</td>
<td>Probably not helpful if O2 saturation ≥92%</td>
</tr>
<tr>
<td></td>
<td>Morphine</td>
<td>2–4 mg IV, q 5–15 min</td>
<td>Watch for respiratory depression</td>
</tr>
<tr>
<td></td>
<td>Nitroglycerin</td>
<td>0.4 mg sublingually; 2% ointment, 1/2–2” transdermally; 10–200 μg/min IV</td>
<td>Watch for hypotension, especially in inferior myocardial infarction</td>
</tr>
<tr>
<td></td>
<td>Metoprolol</td>
<td>2.5–5 mg IV, q 2–5 min, up to 15 mg</td>
<td>Watch for bradycardia, hypotension, heart, block, bronchospasm, worsening HF</td>
</tr>
<tr>
<td></td>
<td>Atenolol</td>
<td>2.5–5 mg IV, q 10 min, up to 10 mg</td>
<td></td>
</tr>
<tr>
<td>Congestive heart failure</td>
<td>Oxygen</td>
<td>As needed to maintain arterial saturation ≥92%</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Furosemide</td>
<td>20–80 mg IV</td>
<td>Watch for hypotension</td>
</tr>
<tr>
<td></td>
<td>Bumetanide</td>
<td>0.5–2 mg IV</td>
<td>Watch for hypotension</td>
</tr>
<tr>
<td></td>
<td>Nitroglycerin</td>
<td>2% ointment, 1/2–2” transdermally; 10–200 μg/min IV</td>
<td>Avoid hypotension</td>
</tr>
<tr>
<td>Hypotension</td>
<td>IV fluids</td>
<td>As needed to maintain adequate perfusion</td>
<td>Watch for worsening heart failure</td>
</tr>
<tr>
<td></td>
<td>Dobutamine</td>
<td>2.5–10 μg/kg/min</td>
<td>Watch for worsening hypotension; may aggravate ischemia</td>
</tr>
<tr>
<td></td>
<td>Dopamine</td>
<td>2–40 μg/kg/min</td>
<td>May worsen ischemia</td>
</tr>
<tr>
<td></td>
<td>Norepinephrine</td>
<td>0.5–30 μg/min</td>
<td>May worsen ischemia</td>
</tr>
</tbody>
</table>

Abbreviation: HF, heart failure.
Therapy of Acute Myocardial Infarction

acutely MI (10). Empiric administration of supplemental oxygen is appropriate, but it is unlikely to improve tissue oxygen delivery if the baseline arterial saturation exceeds 92%. Nitroglycerin is safe in the majority of patients with acute MI, and it is effective in reducing myocardial oxygen demand when administered sublingually, transdermally, or intravenously. Nitrites can occasionally result in a precipitous fall in blood pressure, especially when given sublingually to patients with inferior MI associated with right ventricular involvement (11). Intravenous β-blockers are also effective in relieving chest pain, and both metoprolol and atenolol have been approved for use in patients with acute MI (12,13). As discussed below, contraindications to β-blockers include marked bradycardia, hypotension, moderate or severe heart failure, advanced atrioventricular (AV) block, and significant bronchospastic lung disease.

Heart failure (HF) and hypotension are common complications of acute MI in the elderly, and each is discussed in more detail later in this chapter. They are mentioned briefly here because they are often present when the patient arrives in the emergency room and empiric therapy may be necessary. In most cases, HF occurring in the early stages of acute MI can be effectively treated with a combination of diuretics, nitrites, and supplemental oxygen. In patients who do not respond to these measures, further investigation into the etiology of HF is appropriate. Urgent echocardiography is the most useful noninvasive test in this setting, since it allows assessment of left and right ventricular function, valvular structures, and the pericardium. Sympathomimetic agents such as dobutamine and dopamine are best avoided in the early hours of acute MI because they increase myocardial oxygen demand and may worsen ischemia, but patients with severe HF, particularly when accompanied by hypotension, may require inotropic therapy. In the absence of supraventricular tachyarrhythmias, digitalis has little value in the management of HF associated with acute MI.

Hypotension, particularly when accompanied by HF or impaired tissue perfusion, is a grave prognostic sign warranting prompt intervention. Hypotension without HF should be treated with IV fluids at a rate of 75 to 250 cc/hr until an adequate blood pressure has been restored or until signs of HF develop. In patients with inferior MI, hypotension associated with bradycardia may be due to heightened vagal tone and may respond to 0.5 to 1 mg of subcutaneous or IV atropine. Further investigation is required if the blood pressure fails to respond to fluid resuscitation and both noncardiac (e.g., sepsis, pulmonary embolism, medications) and cardiac causes of hypotension should be considered. In patients with persistent unexplained hypotension, the use of an inotropic or vasopressor agent may be necessary, but the precautions noted above should be borne in mind.

FIBRINOLYTIC THERAPY

In the mid to late 1980s, a series of large randomized clinical trials demonstrated that IV administration of a fibrinolytic agent within 6 to 12 hours of symptom onset in patients with acute MI associated with ST-segment elevation or left bundle branch block led to a significant reduction in short-term and long-term mortality (14–18). These studies ushered in the reperfusion era and revolutionized the approach to treatment of patients with acute coronary syndromes. However, despite the fact that more than 20 years have elapsed since the publication of the first, large trial of fibrinolytic therapy (14), the value of this treatment in patients over age 75 remains controversial.

In 1994, the Fibrinolytic Therapy Trialists’ (FTT) Collaborative Group published a meta-analysis of all major trials, including a subgroup analysis by age (Fig. 1) (19). Although the greatest absolute benefit was seen in patients 65 to 74 years of age (26 fewer
deaths per 1000 treated patients), the benefit was more modest in patients over age 75 years (10 fewer deaths per 1000 treated patients) and failed to achieve statistical significance. Reanalysis of the FTT data, limited to patients presenting within 12 hours of symptom onset with ST-segment elevation or left bundle branch block, showed that among patients aged 75 years or older, mortality was reduced from 29.4% to 26.0% (34 fewer deaths per 1000 treated patients, \( p = 0.03 \)) (20). Moreover, the absolute benefit was similar to that seen in other age groups, and greater than in patients younger than age 55.

In contrast to the FTT analysis, several observational studies have suggested that the use of fibrinolytic therapy in patients over 75 years of age may be associated with adverse outcomes (21–23). In one study, Thiemann et al. examined outcomes in 7864 Medicare patients with acute MI who were suitable candidates for fibrinolytic therapy (21). Among patients 65 to 75 years of age, administration of a fibrinolytic agent was associated with reduced mortality, consistent with the randomized trials. However, among patients aged 76 to 86, mortality was 38% higher in those who received a fibrinolytic drug. In another study, also based on the Medicare database, Berger et al. found that 30-day mortality tended to be higher among patients over 75 years of age receiving fibrinolytic therapy, although the one-year mortality was lower (perhaps reflecting selection bias) (22). In another study, Soumerai et al. examined outcomes of fibrinolytic therapy at 37 Minnesota hospitals and found that fibrinolytic treatment was associated with a 40% higher mortality rate among patients 80 years of age or older (23). The findings of these studies are mitigated somewhat by a report from Stenestrand et al., who examined outcomes in 6891 patients aged 75 years or older hospitalized in Sweden with ST-segment elevation MI from 1995 to 1999 (24). Using propensity score analysis, these investigators found that patients who received fibrinolytic treatment had a 13% lower adjusted relative risk of death or nonfatal cerebral bleeding during a one-year follow-up period (\( p = 0.001 \)). Although the beneficial effects of fibrinolytic therapy were significant in patients 75 to 79 and 80 to 84 years of age, the absolute benefit was lower and no longer statistically significant among patients aged 85 years or older.

One plausible explanation for the apparent discrepancy between the clinical trials and some of the community-based analyses is that criteria for fibrinolysis were strictly regulated in clinical trials, thus ensuring an optimal risk-benefit ratio. Nonadherence to
these criteria in clinical practice may have led to overutilization of fibrinolytic agents in patients who were less-than-ideal candidates for such therapy, resulting in diminished benefit and increased complications.

In summary, data from multiple randomized clinical trials demonstrate that fibrinolytic therapy is beneficial in appropriately selected elderly patients, including those over 75 years of age. However, observational studies indicate that caution is advised in the very elderly, and suggest that strict adherence to established criteria for use of fibrinolytic drugs is essential in patients over age 75 in order to maximize benefit and minimize risk (25).

One factor that limits utilization of fibrinolytic therapy in elderly patients is concern about increased risk of bleeding, particularly intracranial hemorrhage. In the FTT overview of nine large fibrinolytic trials, strokes occurred in 1.2% of patients receiving a fibrinolytic agent, compared to 0.8% in control group patients (absolute difference 0.4%; \( p < 0.0001 \)) (19), and the excess in strokes attributable to fibrinolysis increased with age. Thus, in patients over 75 years of age, the stroke rate was 2.0% in patients receiving fibrinolytic therapy, as compared with 1.2% in controls. Other serious bleeding complications, defined as either life-threatening or requiring transfusion, were relatively uncommon, occurring in 1.1% of patients over 75 years of age receiving fibrinolytic treatment, as compared with 0.5% of control group patients. Notably, the excess in major bleeding complications attributable to fibrinolysis was similar in older and younger patients. Thus, the absolute excess risk for both strokes and major bleeding is less than 1%. Nonetheless, caution is advised when using fibrinolytic agents in elderly patients at increased risk for stroke (e.g., those with prior cerebrovascular disease, severe uncontrolled hypertension, or a markedly increased arterial pulse pressure), as well as in patients at increased risk for serious bleeding (26–28).

Several large trials have compared the effects of different fibrinolytic agents on clinical outcomes (29–32). In the Global Utilization of Streptokinase and tPA for Occluded Arteries (GUSTO)-I trial, which randomized over 40,000 acute MI patients to one of four fibrinolytic regimens, alteplase was associated with lower 30-day mortality than streptokinase in patients up to the age of 85 (32). However, the absolute benefit was small in patients over 75 years of age, and alteplase was associated with a significantly higher risk of intracranial hemorrhage (ICH) compared with streptokinase in this age group (2.1% vs. 1.2%; \( p < 0.05 \)) (33). More recent studies with the newer fibrinolytic agents reteplase and tenecteplase failed to demonstrate a survival advantage of these agents compared with alteplase (34,35), and in the GUSTO-III trial, reteplase was associated with a higher rate of ICH than alteplase (2.5% vs. 1.7%) among patients over 75 years of age (34). Thus, currently available data indicate that the more fibrin-specific fibrinolytic agents (i.e., alteplase, reteplase, tenecteplase) are associated with increased risk of ICH compared with streptokinase in patients over age 75, and the merits of these agents with respect to other clinical outcomes, including mortality, have not been convincingly established in the very elderly.

Streptokinase is administered in a dose of 1.5 million units intravenously over 1 hour, and no dosage adjustment is required for elderly patients. Alteplase should be administered as an initial bolus of 15 mg, followed by 0.75 mg/kg over 30 minutes (not to exceed 50 mg), and 0.5 mg/kg over the next 60 minutes (not to exceed 35 mg) (32). Reteplase is administered in two bolus doses of 10 units at an interval of 30 minutes (34). Tenecteplase is given as a single 30 to 50 mg bolus based on the weight of the patient (35). Aspirin 160 to 325 mg should be given to all patients receiving fibrinolytic therapy. Patients treated with alteplase, reteplase, or tenecteplase should also receive IV heparin to maintain the activated partial thromboplastin time (aPTT) in the range of 50 to 70 seconds.
for the first 24 to 48 hours (36,37). For patients treated with streptokinase, data from the GUSTO study indicate that IV heparin increases bleeding complications but does not improve survival relative to high dose subcutaneous heparin (12,500 U every 12 hours) (32).

PERCUTANEOUS CORONARY INTERVENTION

PCI has several potential applications in the acute MI setting: as a primary reperfusion strategy; as an adjunct to thrombolysis; as a “rescue” procedure for failed thrombolysis; and in the management of recurrent ischemia (38,39).

In several studies, PCI has been shown to be more effective than fibrinolytic therapy in recanalizing the infarct-related coronary artery, with reperfusion rates of over 90% in some series (39). In addition, three randomized trials suggest that PCI is associated with superior outcomes relative to fibrinolytic therapy in older patients with ST-elevation MI (40–42). deBoer et al. randomized 87 acute MI patients over 75 years of age to streptokinase or PCI. At 30 days follow-up, patients allocated to PCI had a reduced risk of death, reinfarction or stroke (p = 0.01), and this benefit persisted for at least one year (40). In another study involving 130 patients with ST-elevation MI 70 years of age or older receiving tissue plasminogen activator or PCI, treatment with PCI was an independent predictor of lower mortality, reinfarction, or revascularization for recurrent ischemia at six months’ follow-up (41). In the largest trial reported to date, Grimes et al. randomized 481 patients aged 70 years or older presenting within 12 hours of onset of ST-elevation MI to fibrinolytic therapy or PCI (42). In this study, PCI was associated with a 55% reduction in death, stroke, or reinfarction relative to fibrinolysis (p = 0.05). Of note, the benefit of PCI was limited to patients 70 to 79 years of age; among 131 patients aged 80 years or older, outcomes did not differ between reperfusion strategies.

The findings of these studies are also supported by subgroup analysis from a systematic overview of 22 randomized trials comparing PCI with fibrinolytic therapy in 6763 patients with acute MI (38). Overall, PCI was associated with a significant 37% reduction in 30-day mortality, and the absolute benefit was greater in patients over age 65 than in younger patients. Moreover, the absolute benefit of PCI increased progressively with age, from 1.0% in patients less than 65 years to 4.2%, 5.1%, and 6.9% in patients of ages 65 to 74, 75 to 84, and 85 or older, respectively (25).

In summary, current data suggest that PCI can be performed safely in elderly patients with acute MI and that it is associated with fewer hemorrhagic strokes and more favorable clinical outcomes compared to fibrinolysis (25). Although present data are insufficient to allow definitive conclusions on primary PCI versus fibrinolytic therapy in patients over 80 years, PCI is an effective therapeutic option in appropriately selected patients and should be strongly considered when fibrinolytic therapy is contraindicated (10,25). In particular, very high-risk elderly patients, such as those with large anterior MIs or severe hemodynamic disturbances, may be most likely to benefit from this approach (43).

The routine use of PCI following fibrinolysis was evaluated in several trials prior to the era of intracoronary stents and none of these studies demonstrated improved outcomes relative to conservative management (44–49). In contrast, two more recent trials reported favorable outcomes among patients who underwent routine stent implantation following fibrinolysis compared with conservative management (50,51). Both of these studies were relatively small and primarily involved younger patients with no subgroup analysis by age. Therefore, the role of routine PCI following successful fibrinolysis in older patients remains uncertain.
Patients who experience recurrent ischemic pain or marked ST-segment changes on a predischarge stress test are at high risk for recurrent ischemic events following hospital discharge. Coronary angiography and revascularization with either PCI or coronary bypass surgery is appropriate in these patients (52) and age per se is not a contraindication to these procedures (10,25,38). Patients with persistent ischemic pain following administration of a fibrinolytic agent, particularly when accompanied by hemodynamic instability (e.g., hypotension or marked HF), are also at high risk for adverse outcomes, and “rescue” PCI appears to improve prognosis in this subgroup (38,39,53,54). Thus, although cardiac catheterization and revascularization are not recommended as routine procedures for all older patients with acute ST-segment elevation MI, they should be strongly considered in patients with persistent chest pain, marked hemodynamic instability, or recurrent ischemia in the early post-MI period (10,25).

ANTITHROMBOTIC AGENTS

Aspirin

Aspirin is of proven benefit in patients with either unstable angina (55,56) or acute MI (16) and it should be considered standard therapy in all patients presenting with acute coronary syndromes (ACS) in the absence of major contraindications. Evidence supporting the use of aspirin for acute MI derives from the second International Study of Infarct Survival (ISIS-2), in which 17,187 patients with suspected MI were randomized to receive either aspirin 162.5 mg or placebo, and either streptokinase 1.5 million units or placebo (16). Overall, patients receiving aspirin experienced a 23% reduction in the risk of vascular death within 35 days of hospitalization, and this effect was independent of whether or not the patient received streptokinase. In 3411 patients over 70 years of age, aspirin was associated with a 21% reduction in vascular deaths (17.6% vs. 22.3%; p < 0.01) (16). With respect to aspirin dosage, available evidence suggests that the minimum effective dose in patients with acute MI is 160 mg, and that doses in excess of 325 mg provide no additional benefit (57). Importantly, the initial dose of aspirin should be administered as soon as possible after presentation, and the nonenteric-coated form should be used to ensure rapid absorption. When possible, the first dose should be chewed rather than swallowed. Following MI, aspirin should be continued indefinitely at a dose of 75 to 325 mg daily or every other day (58,59).

Heparin

Subcutaneous heparin in a dose of 7500 U every 12 hours reduces the risk of venous thromboembolic complications in patients hospitalized with acute MI (60). Since older patients are at increased risk for deep vein thrombosis and pulmonary embolism, prophylaxis against these events is appropriate in this age group.

At present, the value of routine IV heparin for all patients with acute ST-elevation MI remains unproven (61), but several subgroups do appear to benefit (10,62). Patients with large anterior MIs, acute or chronic atrial fibrillation, or severe left ventricular dysfunction with congestive heart failure are at increased risk for mural thrombus formation and embolization. Intravenous heparin at doses adjusted to maintain the aPTT at 1.5 to 2 times the control value appears to reduce arterial thromboembolism in patients with large anterior MIs (60,62,63), and routine heparinization is appropriate (10). Patients with atrial fibrillation should be anticoagulated with heparin or warfarin, but the value of systemic anticoagulation in patients with severe left ventricular dysfunction is unproven,
and its use in this situation should be individualized (10). Patients who experience recurrent ischemia during the first few days after MI are at increased risk for infarct extension, and IV heparin is recommended (10,60).

**Low-molecular-weight Heparin**

Compared with unfractionated IV heparin, low-molecular-weight heparins (LMWHs) offer several advantages: once or twice daily subcutaneous dosing, no need to monitor aPTTs, and fewer side effects (especially thrombocytopenia). In a meta-analysis of 14 trials involving 25,280 patients with ST-elevation MI receiving fibrinolytic therapy and aspirin, Eikelboom et al. reported that relative to placebo, LMWH reduced the risk of reinfarction by 28% and death by 10%, but increased the risk of major bleeding and intracranial bleeding (64). Compared with unfractionated heparin, LMWH reduced the risk of reinfarction by 45%, increased the risk of minor bleeding, and had no effect on mortality or major bleeding. Subgroup analyses by age were not reported. In addition, since all patients in these trials were treated with a fibrinolytic agent, the findings may not be applicable to patients receiving PCI or no reperfusion therapy. Further, careful attention to dosing of LMWH is required in older patients with decreased renal function, since excess dosing has been associated with an increased risk for major bleeding. (65)

Based on available data, current guidelines recommend unfractionated heparin in preference to LMWH in patients with ST-elevation MI undergoing reperfusion therapy with either PCI or a fibrinolytic agent (10). In other patients for whom antithrombotic therapy is warranted, either unfractionated heparin or LMWH may be used.

**Glycoprotein IIb/IIIa Inhibitors**

The glycoprotein (GP) IIb/IIIa inhibitors are potent antiplatelet agents that block the final common pathway leading to platelet aggregation. Three GP IIb/IIIa inhibitors—abciximab, eptifibatide, and tirofiban—have been shown to improve outcomes in patients with ACS, primarily in the setting of non-ST-elevation MI (66–70). However, although the benefits of GP IIb/IIIa inhibitors in patients up to the age of 75 years are similar to those in younger patients, the value of these agents in older patients is less clear. For example, in a trial involving over 10,000 patients, eptifibatide reduced the risk of death or nonfatal MI in patients up to the age of 79, but there was an increase in event rates among patients over 80 years of age receiving eptifibatide (70). In another study involving a smaller number of patients ($n = 1915$), tirofiban was associated with improved outcomes in patients younger or older than age 65, but outcomes for patients over 75 years were not reported (69). More recently, a retrospective analysis from the Intracoronary Stenting and Antithrombotic Regimen: Rapid Early Action for Coronary Treatment (ISAR-REACT) trial found that although abciximab reduced the risk of major coronary events by 43% in ACS patients under age 70 undergoing PCI, there was no benefit in patients age 70 or older (71). Nonetheless, on the basis of current evidence, the addition of abciximab to aspirin and heparin is recommended for patients with acute ST-elevation MI undergoing cardiac catheterization and PCI (10). In patients with ST-elevation MI not undergoing PCI, routine use of GP IIb/IIIa inhibitors is not recommended (10). Furthermore, the risk of bleeding complications associated with these agents increases with age, which may negate the clinical benefit of GP IIb/IIIa inhibitors in the very elderly.
Thienopyridines

Ticlopidine and clopidogrel are thienopyridine derivatives that inhibit platelet aggregation through multiple mechanisms; both are more effective antiplatelet agents than aspirin. Although both drugs reduce restenosis rates following coronary stent implantation, clopidogrel is preferred because of superior efficacy and safety (72). In addition, the combination of clopidogrel and aspirin has been shown to reduce the risk of cardiovascular death, MI, or stroke by about 20% compared to aspirin alone during the 12-month period following hospitalization for unstable angina or non-ST-elevation MI, with similar absolute benefits in patients younger or older than age 65 (73). Current guidelines recommend clopidogrel for all patients with ACS undergoing PCI (10). Clopidogrel should be continued for at least one month following placement of a bare metal stent and for at least 9 to 12 months following placement of a drug-eluting stent. If feasible, clopidogrel should be discontinued five to seven days prior to coronary bypass surgery because of an increased risk for perioperative bleeding.

Warfarin

Long-term anticoagulation with warfarin has been shown to reduce the risk of reinfarction and cardiac death in post-MI patients, including the elderly (74–76), and recent studies indicate that warfarin, with or without aspirin, is superior to aspirin alone (77,78). However, the addition of warfarin to aspirin increases the risk of bleeding, and this risk is greatest in elderly patients. Current indications for warfarin in the post-MI setting include allergy to aspirin, chronic or paroxysmal atrial fibrillation, the presence of a mechanical prosthetic heart valve, or active thromboembolic disease. Anticoagulation for a minimum of three months is also recommended for patients with a left ventricular mural thrombus following acute MI (10). Warfarin may also be considered in other patients deemed to be at high risk for left ventricular thrombus or recurrent coronary events.

Bleeding Complications

An important consideration when using antithrombotic therapy in older patients is the increased bleeding risk accompanying the administration of multiple antithrombotic agents (e.g., aspirin, heparin, clopidogrel, and a glycoprotein IIb/IIIa inhibitor). Although there is no precise method to quantify this risk and to accurately assess the risk–benefit ratio of using multiple antithrombotic drugs in an individual patient, it is worth noting that in a recent study to evaluate the effects of LMWH and abciximab (a glycoprotein IIb/IIIa inhibitor) in patients receiving tenecteplase for acute MI, abciximab was associated with a marked increase in bleeding complications among patients over 75 years of age, resulting in overall worse outcomes in this age group (79). In addition, advanced age has been associated with increased risk for excessive dosing and major bleeding complications in patients with ACS treated with heparin, LMWH, or GP IIb/IIIa inhibitors (65). Thus, the benefits of aggressive antithrombotic therapy in reducing recurrent ischemic events must be carefully balanced against the risk of serious bleeding complications, particularly in the very elderly.

β-BLOCKADE

Most of the major trials evaluating β-blockers for the treatment of acute MI were conducted prior to the reperfusion era. However, since most elderly patients with acute MI do not undergo primary PCI or thrombolysis (80,81), the results of these earlier trials remain applicable.
Table 2 summarizes data from three large randomized trials of early IV β-blockade in patients with suspected MI (12,13,82). In the ISIS-1 study, administration of IV atenolol followed by oral therapy was associated with a 15% reduction in vascular deaths within the first seven days (12). Among 5222 patients 65 years of age or older, there was a 23% mortality reduction (\( p = 0.001 \)) (12). Similarly, in two trials using IV metoprolol, older patients benefited more than younger patients (13,82). In pooling the results of these three trials, mortality was reduced by 23% in older patients (\( p = 0.005 \)), but by only 5% in younger patients (\( p = \text{not significant} \)). These data clearly indicate that older patients, who are at higher risk for adverse outcomes, derive proportionately greater benefit from early β-blocker therapy than younger patients. As a result, IV β-blockers should not be withheld on the basis of age.

The value of IV β-blockade in combination with fibrinolytic therapy was assessed in the second Thrombolysis in Myocardial Infarction trial (TIMI-II) (83,84). In this study, 1434 patients with acute MI were treated with alteplase and then randomized to receive IV metoprolol or placebo. Although there was no difference in hospital or six-week mortality, patients receiving metoprolol experienced significantly fewer nonfatal ischemic events during follow-up. These findings provide support for the use of early IV β-blockade as an adjunct to fibrinolysis in patients with acute MI.

More recently, Wienbergen et al. examined the impact of early β-blocker therapy in 17,809 consecutive patients with ST-elevation MI enrolled in the German Maximal Individual Therapy of Acute Myocardial Infarction PLUS (MITRA PLUS) registry (85). After adjusting for covariates, early β-blocker treatment was associated with a 30% lower hospital mortality, and the greatest benefit was seen in high-risk patients, including those over age 65.

Despite these favorable results, recently reported findings from the Clopidogrel and Metoprolol in Myocardial Infarction Trial (COMMIT) have raised new questions about the value of IV β-blockers in patients with acute MI (86). In this study, 45,852 patients with acute MI, 93% of whom had ST-elevation or left bundle branch block, were

### Table 2 Mortality in Three Large Trials of Intravenous β-Blockade

<table>
<thead>
<tr>
<th></th>
<th>Number</th>
<th>Active</th>
<th>Control</th>
<th>Difference</th>
<th>% Change</th>
<th>( p ) value</th>
</tr>
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<tbody>
<tr>
<td><strong>Atenolol</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ISIS-1 (12)a</td>
<td>16,027</td>
<td>10,805</td>
<td>2.5</td>
<td>2.6</td>
<td>−0.1</td>
<td>−4.0 NS</td>
</tr>
<tr>
<td>&lt;65 yr</td>
<td></td>
<td></td>
<td>2.6</td>
<td></td>
<td>−0.1</td>
<td>−4.0 NS</td>
</tr>
<tr>
<td>≥65 yr</td>
<td>5,222</td>
<td>6.8</td>
<td>8.8</td>
<td></td>
<td>−2.0</td>
<td>−22.7 0.001</td>
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<tr>
<td><strong>Metoprolol</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Goteborg (82)a</td>
<td>1,395</td>
<td>917</td>
<td>4.5</td>
<td>5.7</td>
<td>−1.2</td>
<td>−21.1 NS</td>
</tr>
<tr>
<td>&lt;65 yr</td>
<td></td>
<td>478</td>
<td>8.1</td>
<td>14.8</td>
<td>−6.6</td>
<td>−45.0 0.03</td>
</tr>
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<td>65–74 yr</td>
<td></td>
<td>2,965</td>
<td>1.9</td>
<td>1.8</td>
<td>+0.1</td>
<td>+3.1 NS</td>
</tr>
<tr>
<td>MIAMI (13)a</td>
<td>5,778</td>
<td>2,813</td>
<td>6.8</td>
<td>8.2</td>
<td>−1.5</td>
<td>−17.8 NS</td>
</tr>
<tr>
<td>&lt;60 yr</td>
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<td>8.2</td>
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<td>−1.5</td>
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<td>61–74 yr</td>
<td></td>
<td></td>
<td>6.8</td>
<td></td>
<td>−1.5</td>
<td>−17.8 NS</td>
</tr>
<tr>
<td><strong>Pooled totals</strong></td>
<td>23,200</td>
<td>14,687</td>
<td>2.5</td>
<td>2.6</td>
<td>−0.1</td>
<td>−5.0 NS</td>
</tr>
<tr>
<td>Younger</td>
<td></td>
<td></td>
<td>2.6</td>
<td></td>
<td>−0.1</td>
<td>−5.0 NS</td>
</tr>
<tr>
<td>Older</td>
<td>8,513</td>
<td>6.9</td>
<td>8.9</td>
<td></td>
<td>−2.1</td>
<td>−23.2 0.0005</td>
</tr>
</tbody>
</table>

*Reference.

**Abbreviations:** ISIS-1, First International Study of Infarct Survival; MIAMI, Metoprolol in Acute Myocardial Infarction; NS, not significant.
randomized to IV metoprolol or placebo. Overall, metoprolol did not reduce the risk of death, reinfarction, or cardiac arrest, but the risk of cardiogenic shock was increased by 30% in patients randomized to metoprolol. Among 11,934 patients aged 70 years or older enrolled in the trial, hospital mortality was 13.6% with metoprolol compared with 13.3% in the placebo group.

Current guidelines recommend prompt administration of an oral β-blocker to all patients with acute MI in the absence of contraindications (10). Intravenous β-blocker therapy may be considered in stable patients with tachycardia or hypertension who have no contraindication to β-blocker therapy.

The long-term use of β-blockers for secondary prevention following acute MI has been extensively investigated, and Table 3 summarizes data from three of the largest and most frequently cited trials (82,87–91). Notably, reductions in mortality and reinfarction during long-term therapy were at least as great in the elderly as in younger patients. More recently, carvedilol was associated with a 23% reduction in mortality relative to placebo in patients with a left ventricular ejection fraction less than or equal to 40% following acute MI (92). In addition, observational studies indicate that the survival benefits of β-blockers following MI appear to extend to patients over 75 years of age (93–95). In one study, covariate-adjusted two-year mortality rates in patients prescribed β-blockers, relative to those who were not, were 50% lower among patients 65 to 74 years of age, 44% lower in patients age 75 to 84, and 28% lower in patients over age 85 (93). β-Blockers are also highly cost-effective in all age groups (96). Thus, β-blockers are recommended for all patients following acute MI in the absence of contraindications.

At the present time, only atenolol and metoprolol have been approved for IV use in the acute MI setting. The recommended dose for intravenous atenolol is two 5 mg boluses at an interval of 10 minutes. Oral atenolol 50 mg every 12 hours should be initiated 10 minutes after the second IV dose. For metoprolol, the recommended IV dose is 15 mg (three 5 mg doses at 2 minute intervals). Oral metoprolol 25 to 50 mg every 6 hours should be started 15 minutes after the last IV dose, progressing to 100 mg twice daily in

| Table 3  | Mortality in Three Large Trials of Long-term β-Blockade |
|-----------------|-----------------|-----------------|-----------------|-----------------|
| Mortality (%)   | Number | Active | Control | Difference | % Change | p value |
| Propranolol     |        |        |        |            |         |         |
| BHAT (87,88)a   | 3,837  | 6.0    | 7.4    | −1.4       | −18.7    | NS      |
| 30–59 yr        | 2,588  | 4.0    | 5.4    | −1.4       | −14.1    | NS      |
| 60–69 yr        | 1,249  | 9.7    | 14.7   | −5.0       | −33.7    | 0.01    |
| Timolol         |        |        |        |            |         |         |
| Norwegian (89,90,91)a | 1,884  | 5.0    | 7.4    | −2.4       | −26.4    | 0.003   |
| <65 yr          | 1,149  | 9.0    | 11.4   | −2.4       | −20.9    | 0.003   |
| 65–75 yr        | 735    | 8.0    | 15.3   | −7.3       | −47.8    | 0.003   |
| Metoprolol      |        |        |        |            |         |         |
| Goteborg (82)a  | 1,395  | 5.5    | 7.6    | −2.2       | −28.3    | 0.004   |
| <65 yr          | 917    | 4.5    | 5.7    | −1.2       | −21.1    | NS      |
| 65–74 yr        | 478    | 8.1    | 14.8   | −6.6       | −45.0    | 0.03    |
| Pooled totals   | 7,116  | 5.5    | 7.6    | −2.2       | −28.3    | 0.004   |
| Younger         | 4,654  | 5.5    | 7.6    | −2.2       | −28.3    | 0.004   |
| Older           | 2,462  | 8.9    | 14.9   | −6.0       | −40.1    | 0.00001 |

aReference.
Abbreviations: BHAT, β-Blocker Heart Attack Trial; NS, not significant.
24 to 48 hours. In very elderly patients, it may be advisable to reduce the dosages of both the agents.

Contraindications to the use of IV β-blockers include marked sinus bradycardia (heart rate < 45/min), systolic blood pressure less than 100 mmHg, marked first-degree AV block (PR interval ≥ 0.24 seconds) or higher levels of block, moderate or severe HF, active wheezing, or a history of significant bronchospastic pulmonary disease. Mild HF and chronic lung disease without bronchospasm are not contraindications to β-blocker therapy.

Propranolol, metoprolol, timolol, and carvedilol have all been approved for long-term use following MI. Recommended daily dosages for these agents are as follows: propranolol 180 to 240 mg, metoprolol 200 mg, timolol 20 mg, and carvedilol 50 mg. Elderly patients may require lower doses to avoid adverse effects, and there are data suggesting that lower doses may be as effective as higher ones for reducing mortality in older patients (97). Contraindications to oral β-blockers are similar to those listed for the IV drugs.

NITRATES

Nitrates are widely used in the treatment of acute MI (98), but two large studies (GISSI-3 and ISIS-4) failed to confirm a beneficial effect when nitrates were initiated within 24 hours of MI onset (99,100). However, among 5234 patients aged 70 years or older enrolled in GISSI-3, the combined endpoint of death or severe left ventricular dysfunction at 6 months follow-up was significantly reduced by nitroglycerin (odds ratio 0.88; \( p = 0.04 \)) (101). This finding, coupled with the fact that both GISSI-3 and ISIS-4 demonstrated that nitrates can be administered safely to the majority of older patients, suggests that the continued use of nitrates for treating ischemic pain and peri-infarctional heart failure is appropriate. Routine use of nitrates in elderly patients without pain or pulmonary congestion is of unproven value. Nitrates are contraindicated in patients with right ventricular infarction or systolic blood pressure less than 90 mmHg in the setting of acute MI (10).

CALCIUM ANTAGONISTS

Calcium channel blockers have been widely studied in both the acute MI and post-MI settings (102,103). At present, there is no evidence that treatment with calcium antagonists is beneficial in patients with acute MI, and the use of short-acting calcium antagonists may be harmful (102). One relatively small study showed that diltiazem 60 to 90 mg q.i.d. initiated 24 to 72 hours after admission for non-ST-elevation MI reduced the rate of reinfarction during short-term follow-up, but there was no effect on mortality (104). In another study, long-term diltiazem administration following MI did not affect overall mortality, but a modest benefit was seen in the subgroup of patients with preserved left ventricular function and no HF (105). Similar results have been reported with long-term verapamil use in post-MI patients (106), although a later study failed to confirm these findings (107). Thus, calcium antagonists are not recommended for routine use in acute MI patients, but administration of diltiazem or verapamil is reasonable in patients with preserved ventricular function and no HF who are not candidates for β-blockade (10). Calcium channel blockers are contraindicated in patients with acute MI complicated by heart failure or left ventricular systolic dysfunction.
ANGIOTENSIN CONVERTING ENZYME INHIBITORS

Early administration of an ACE inhibitor to acute MI patients has been evaluated in several large trials. The first of these, Cooperative New Scandinavian Enalapril Survival Study (CONSENSUS-2), was discontinued after 6000 patients were enrolled due to a higher frequency of adverse outcomes in patients receiving IV enalapril (108). Moreover, patients over 70 years of age experienced an increased incidence of serious hypotension. In contrast, the GISSI-3 and ISIS-4 trials reported small but statistically significant reductions in mortality in patients receiving oral captopril or lisinopril within 24 hours of MI onset (99,100). In addition, patients 70 years or older treated with lisinopril in GISSI-3 experienced a 14% reduction in the combined endpoint of death or severe left ventricular dysfunction at 6 months follow-up ($p = 0.01$) (101). More recently, the Survival of Myocardial Infarction Long-term Evaluation (SMILE) investigators randomized 1556 patients with anterior MI who were not candidates for fibrinolytic therapy to either the ACE inhibitor zofenopril or to placebo within the first 24 hours after symptom onset (109). The incidence of death or severe heart failure at 6 weeks follow-up was reduced 34% by zofenopril, and this benefit was maintained for one year. Moreover, the absolute benefit was threefold greater in individuals over 65 years of age compared with younger patients (109).

The applicability of the above findings to the general MI population is unclear, since the small benefit seen in the largest trials (absolute mortality reduction less than 1%) (99,100) may reflect a larger benefit in some patients (e.g., those with anterior MI or significant left ventricular dysfunction), but no benefit or even harm in other subgroups. At the present time, early administration of an oral ACE inhibitor is recommended in hemodynamically stable patients with anterior MIs, as well as in patients with HF or a left ventricular ejection fraction of less than 40% in the absence of hypotension (systolic blood pressure < 100 mmHg) or other contraindications (10). In other cases, early ACE inhibitor therapy is optional (10).

The value of ACE inhibitors in post-MI patients with significant left ventricular dysfunction (ejection fraction < 40%) or clinical HF has been well established by the Salvage and Ventricular Enlargement (SAVE) (110) and Acute Infarction Ramipril Efficacy (AIRE) trials (111,112). In SAVE, captopril reduced mortality and the occurrence of other cardiac events during an average follow-up of 42 months in asymptomatic or minimally symptomatic patients with left ventricular dysfunction after MI (ejection fraction $\leq 40\%$) (110). In AIRE, ramipril produced similar effects in post-MI patients with clinical heart failure (111,112). Therapy was initiated 3 to 16 days after MI in SAVE (mean, 11 days), and 2 to 10 days after MI in AIRE (mean, 5 days). The maximum dose of captopril in SAVE was 50 mg t.i.d., while the target dose of ramipril in AIRE was 5 mg b.i.d. Importantly, in both SAVE and AIRE, the beneficial effects of therapy were most pronounced in elderly patients (110,111). In 783 patients over 65 years of age enrolled in SAVE, mortality was reduced by 23% with captopril (27.9% vs. 36.1%; $p = 0.017$); by comparison, patients under age 65 experienced a statistically insignificant 9% mortality reduction (16.6% vs. 18.3%) (110). Similarly, ramipril significantly decreased mortality in patients over age 65 enrolled in AIRE, but not in younger patients (111). The Heart Outcomes Prevention Evaluation (HOPE) study also showed that the ACE inhibitor ramipril in a dose of 10 mg once daily reduced mortality and major vascular events in a broad range of patients 55 years of age or older with established vascular disease (including chronic coronary artery disease) or diabetes (113). Similarly, the European trial on reduction of cardiac events with perindopril in stable coronary artery disease (EUROPA) randomized 13,655 patients with stable coronary artery disease, of
whom 64% had prior MI, to perindopril or placebo (114). After a mean follow-up period of 4.2 years, perindopril was associated with a 20% reduction in cardiovascular death, MI, or cardiac arrest, and the benefits were similar in younger and older patients. These findings are also supported by a retrospective analysis of 14,129 patients 65 years of age or older hospitalized with acute MI (115). In this study, patients discharged on an ACE inhibitor had a covariate-adjusted one-year mortality rate that was 15% lower than in patients not receiving an ACE inhibitor, including a 27% lower mortality in patients over the age of 80.

In summary, ACE inhibitors are indicated for all patients following acute MI, including the elderly, in the absence of contraindications (10). The therapy should be initiated within the first few days in hemodynamically stable patients, but may be deferred in other cases. Dosages should be titrated to those proven to be effective in clinical trials, while monitoring blood pressure, renal function, and serum potassium levels at regular intervals.

**ANGIOTENSIN RECEPTOR BLOCKERS**

Angiotensin receptor blockers (ARBs) bind to the angiotensin1 (AT1) receptor on the cell membrane, thereby inhibiting the effects of angiotensin II. ARBs are associated with less cough than ACE inhibitors, but the rates of hyperkalemia and worsening renal function are similar with both drug classes. Two large trials have evaluated ARBs in the post-MI setting. In the Optimal Trial in Myocardial Infarction with Angiotensin II Antagonist Losartan (OPTIMAAL), patients 50 years of age or older with acute MI accompanied by heart failure, anterior Q waves on ECG, or an ejection fraction less than 35% were randomized to losartan or captopril and followed for an average of 2.7 years (116). Mortality was nonsignificantly higher in the losartan group (18.2% vs. 16.4%, \( p = 0.069 \)), with similar outcomes in older and younger subjects. In the Valsartan in Acute Myocardial Infarction Trial (VALIANT), 14,703 patients with acute MI were randomly assigned to receive captopril, valsartan, or both the drugs and followed for a median of 25 months (117). Mortality was similar in all three arms, but side effects and withdrawals were more common in patients randomized to combination therapy. More than half of the patients in VALIANT were 65 years of age or older, 3160 patients were aged 75 years or older, and outcomes with respect to the three treatment groups were similar across age categories, including patients over age 85 (118).

On the basis of currently available evidence, ACE inhibitors remain the preferred agents in patients with recent acute MI, including the elderly (10). ARBs are indicated in patients with HF or left ventricular systolic dysfunction who are intolerant to ACE inhibitors. In addition, combination therapy with an ACE inhibitor and an ARB may be considered in patients with persistent symptomatic HF and an ejection fraction less than 40%.

**ALDOSTERONE ANTAGONISTS**

In the Eplerenone Post-acute myocardial infarction Heart Failure Efficacy and Survival Study (EPHESUS), the selective aldosterone antagonist eplerenone reduced mortality by 17% in patients with left ventricular dysfunction (ejection fraction \( \leq 40\% \)) and HF after myocardial infarction (119). However, the benefit of eplerenone was attenuated in patients 65 years of age or older, and there was no apparent benefit in patients aged 75 years or older. In addition, the risk of hyperkalemia was higher in older subjects. Therefore, the value of eplerenone in elderly patients following acute MI remains unproven (25).
MAGNESIUM

Although several relatively small studies suggested that selected patients with acute MI, including the elderly, might benefit from routine administration of magnesium (120, 121), two large randomized trials failed to confirm a beneficial effect (100, 122). Therefore, the routine use of IV magnesium in elderly patients with acute MI is not recommended (10).

ANTIARRHYTHMIC AGENTS AND DEVICES

The administration of prophylactic lidocaine to patients with acute MI was once a common practice. However, a meta-analysis suggested that lidocaine does not improve survival and may increase the incidence of asystolic cardiac arrest (123). Moreover, elderly patients hospitalized with acute MI appear to be at lower risk for primary ventricular fibrillation than younger patients (124), and toxicity from lidocaine is more common in the elderly. Thus, the routine use of lidocaine in elderly patients with acute MI is not recommended (10).

Intravenous amiodarone is more effective than lidocaine in the treatment of life-threatening ventricular arrhythmias in the setting of acute ischemic heart disease, and two trials have addressed the role of prophylactic oral amiodarone in the treatment of high-risk post-MI patients (125, 126). In these studies, which involved a total of 2688 patients, amiodarone reduced the incidence of arrhythmic death by 35% to 38%, but there was no difference in total mortality. In one study, the absolute reduction in arrhythmic deaths was greatest in patients over 70 years of age (126). A subsequent meta-analysis, based on data from 13 amiodarone trials, found that amiodarone was associated with a 13% reduction in total mortality (\( p = 0.03 \)) and a 29% reduction in arrhythmic deaths (\( p = 0.0003 \)) (127). In patients over 65 years of age, amiodarone reduced arrhythmic deaths by 32%, but total mortality was reduced by only 8% (not significant) (127). Based on amiodarone’s apparent lack of efficacy for reducing total mortality and the high side effect profile associated with this drug, prophylactic use of amiodarone in high-risk patients following acute MI is not recommended.

An implantable cardioverter-defibrillator (ICD) is indicated in patients who develop ventricular fibrillation or hemodynamically significant sustained ventricular tachycardia more than 48 hours after acute MI (10). The value of prophylactic ICD insertion in other post-MI patients is uncertain because of conflicting results from clinical trials (128–130). In the most recent study, 674 patients with a left ventricular ejection fraction less than or equal to 35% and evidence for impaired cardiac autonomic function were randomized to receive an ICD or no ICD 6 to 40 days after acute MI (130). Although ICD implantation reduced the risk of arrhythmic death by 58%, there was no difference in total mortality during a mean follow-up period of 30 months. Thus, routine implantation of an ICD in post-MI patients is not warranted at the present time. Ongoing studies should clarify whether ICDs are beneficial in selected patients following MI, including the elderly.

STATINS

Statins have been shown to reduce long-term mortality and morbidity in patients up to 85 years of age with vascular disease (131, 132). In addition, early administration of high-dose statin therapy within the first 96 hours of acute MI has been shown to reduce the risk of recurrent ischemic events during the 4-month period following hospital discharge, with similar effects in older and younger patients (133). More recently, the Pravastatin or
Atorvastatin Evaluation and Infection Therapy (PROVE-IT) trial demonstrated that high-dose atorvastatin was more effective than standard dose pravastatin in reducing the composite endpoint of death, MI, hospitalization for unstable angina, coronary revascularization, or stroke following acute MI (134). The benefit of high-dose atorvastatin appeared to be limited, however, to patients less than 65 years of age. In another trial, early initiation of simvastatin 40 mg with a subsequent increase to 80 mg did not significantly improve outcomes relative to deferred treatment with simvastatin 20 mg in 4497 patients hospitalized with ACS, and the results were similar in younger and older patients (135). On the basis of the totality of evidence, prescription of statin therapy is recommended for all patients with acute MI regardless of age or baseline lipid profile (10,25).

MANAGEMENT OF COMPLICATIONS

Elderly patients are at increased risk for several major complications of acute MI, including HF, hypotension, supraventricular arrhythmias, conduction disturbances, myocardial rupture, and cardiogenic shock. In general, the management of these complications is similar in older and younger patients. In the following sections, the treatment of each of these complications is briefly reviewed, with special attention to the elderly.

Heart Failure

Several factors predispose the elderly patient with acute MI to the development of HF, including an increased incidence of prior MI, higher prevalence of multivessel disease, impaired diastolic relaxation, reduced contractile reserve, and an increased prevalence of comorbid illnesses, both cardiac (e.g., aortic stenosis) and noncardiac (e.g., renal insufficiency) (136). As a result, HF occurs in approximately 50% of older patients with acute MI (7), and HF is often the presenting manifestation of MI in the elderly (137).

The initial treatment of HF includes supplemental oxygen, diuretics, and nitrates. In more severe cases, morphine should also be given. Once therapy has been initiated, it is essential to determine the etiology of HF, which is frequently multifactorial in elderly patients. Commonly occurring factors that may contribute to HF in the elderly include persistent or recurrent ischemia, extensive myocardial damage, aortic or mitral valve disease (especially aortic stenosis or mitral regurgitation), arrhythmias (especially atrial fibrillation), uncontrolled hypertension, diastolic dysfunction due to left ventricular hypertrophy, inappropriate bradycardia, mechanical complications (e.g., papillary muscle rupture or ventricular septal perforation), severe renal insufficiency, and medications (e.g., β-blockers, calcium antagonists, and antiarrhythmic agents). In most cases, an echocardiogram with Doppler studies, in conjunction with a careful review of the patient’s medications and laboratory data, will be sufficient for determining the pathogenesis of HF (10). Occasionally, supplemental studies, such as pulmonary artery catheterization or left ventricular angiography, may be necessary (10).

Once the etiology has been established, an effort should be made to correct treatable disorders and to reduce the dose or discontinue offending medications. If HF persists despite aggressive diuresis, placement of a pulmonary artery catheter should be considered as an aid to diagnosis and therapy. When indicated, treatment with an inotropic agent and/or an IV vasodilator should be instituted. Dobutamine is the most frequently used IV inotrope for treating severe left ventricular dysfunction, but dobutamine
may be less effective in the elderly due to an age-related decline in \( \beta \)-adrenergic responsiveness (138,139). Phosphodiesterase inhibitors such as milrinone have theoretical advantages over sympathomimetic agents in coronary patients because they augment cardiac output without increasing myocardial oxygen demand (140). Nonetheless, in elderly patients with severe HF without recent MI, dobutamine appears to be at least as effective as a phosphodiesterase inhibitor (141).

Nitroglycerin, nitroprusside, and nesiritide are the most commonly used IV vasodilators, but nitroglycerin is the only one recommended for treatment of HF in the setting of acute MI (10). Intravenous nitroglycerin has a very short half-life, which allows rapid drug titration. Hypotension is the most common serious adverse effect, so blood pressure should be monitored closely. In patients with acute decompensated HF, nesiritide is more effective than nitroglycerin in relieving pulmonary congestion and reducing dyspnea (142), but data on the use of nesiritide in patients with acute MI are very limited, and there is concern that nesiritide may be associated with worsening renal function and increased short-term mortality (143,144). Intravenous enalaprilat is another alternative to nitroglycerin and may be useful in patients who are likely to require long-term ACE inhibition. However, enalaprilat may also induce hypotension and renal dysfunction, and it offers no clear advantage over conventional agents in the acute MI setting (145).

Patients who fail to respond to the above measures have refractory HF, and the prognosis is grave unless a correctable problem, such as a ventricular aneurysm, can be identified. Additional interventions that may help stabilize patients with refractory HF include endotracheal intubation with assisted ventilation and placement of an intra-aortic balloon pump. Such therapies are usually appropriate only in patients with potentially reversible pathology.

**Hypotension**

Hypotension in the setting of acute MI usually reflects a low cardiac output state arising from extensive myocardial damage, intravascular volume depletion, right ventricular infarction, valvular dysfunction (especially mitral regurgitation), pericardial effusion, or arrhythmias (both tachycardias and bradycardias). Other factors that may contribute to hypotension in elderly patients include preexisting cardiac conditions such as aortic stenosis or cardiomyopathy, ventricular septal perforation, aortic dissection, sepsis, bleeding (e.g., from fibrinolytic therapy or catheterization), and medications. The cause of hypotension is frequently multifactorial, and it is incumbent upon the physician to consider all potential etiologies and to perform appropriate diagnostic investigations as indicated. If the history, physical examination, and laboratory data fail to provide an explanation, echocardiography should be performed promptly (10). If hypotension persists or if the etiology remains unexplained, pulmonary artery catheterization is indicated (10).

In the absence of HF, intravascular volume expansion is the appropriate initial treatment for hypotension. Subsequent therapy will depend on the response to fluid administration and the underlying etiology. Patients who fail to respond to IV fluids or who have coexistent HF may require pulmonary artery catheterization (10). On the basis of the hemodynamic findings and the severity of hypotension, treatment with sympathomimetic agents such as dobutamine, dopamine, or norepinephrine may be necessary to maintain organ perfusion. Other supportive measures include assisted ventilation and intra-aortic balloon counterpulsation (10). It is important to emphasize that all of these interventions are palliative, and unless the underlying etiology of hypotension can be corrected, the prognosis is grave.
Arrhythmias and Conduction Disturbances

Elderly patients with acute MI are at increased risk for supraventricular arrhythmias, particularly atrial fibrillation, and for conduction disturbances, including bundle branch block and high-degree AV block. The incidence of ventricular tachycardia is similar in older and younger patients, but primary ventricular fibrillation occurs less frequently in the elderly (124), possibly reflecting reduced β-adrenergic responsiveness in this age group.

New-onset atrial fibrillation following acute MI usually results from atrial distension due to an increase in ventricular diastolic pressure. Contributing factors may include mitral or tricuspid regurgitation, atrial infarction, pericarditis, electrolyte abnormalities (particularly hypokalemia), and medications (e.g., inotropic agents, bronchodilators). Because elderly patients frequently have preexisting diastolic dysfunction and an increased reliance on atrial contraction to augment ventricular filling (the “atrial kick”) (136), atrial fibrillation often precipitates HF or a low cardiac output state.

Treatment of atrial fibrillation includes correcting any reversible abnormalities (e.g., hypokalemia), controlling the ventricular rate, and restoring sinus rhythm. In patients who are hemodynamically stable, rate control with β-blockers or rate-lowering calcium channel blockers (i.e., diltiazem or verapamil) is appropriate. In most cases, heparinization to maintain the activated partial thromboplastin time (aPTT) in the range of 50 to 70 seconds is also indicated. Although effective rate control often results in spontaneous conversion to sinus rhythm, if atrial fibrillation persists longer than 24 hours, pharmacological or electrical cardioversion should be considered. Antiarrhythmic agents commonly used in the cardioversion of recent-onset atrial fibrillation include amiodarone, sotalol, and ibutilide. All of these agents are negatively inotropic and should be used with caution in the presence of significant left ventricular dysfunction. In patients who exhibit hypotension, severe HF, or organ hypoperfusion attributable to atrial fibrillation, immediate direct current (DC) cardioversion is the treatment of choice (10). Patients should be sedated before cardioversion is attempted, and an initial energy level of 200 J is appropriate (10). Patients with persistent or chronic atrial fibrillation should receive long-term antithrombotic therapy (146). Warfarin remains the preferred agent in this setting, but aspirin is an acceptable, albeit less effective alternative in patients with major contraindications to warfarin (146).

The treatment of peri-infarctional ventricular tachyarrhythmias is similar in older and younger patients and will not be reviewed here. In general, initial therapy should follow the Advanced Cardiac Life Support (ACLS) guidelines (147), and subsequent therapy should be individualized on the basis of symptoms, severity of arrhythmia, and other factors, such as left ventricular function. Similarly, the treatment of bradyarrhythmias and conduction disturbances does not differ in younger and older patients. In general, temporary pacing (transthoracic or transvenous) should be considered in patients with symptomatic or hemodynamically compromising bradyarrhythmias unresponsive to atropine, in patients with new bundle branch block, and in patients with second- or third-degree infranodal block complicating anterior MI. The ACLS guidelines should be followed in treating life-threatening bradyarrhythmias such as asystole (147).

Right Ventricular Infarction

Right ventricular infarction occurs in up to 50% of patients with inferior MI, with somewhat higher frequency in older than in younger patients (148). The pathophysiology, clinical features, and treatment of right ventricular infarction have previously been reviewed and will not be discussed in detail here (11). However, it is worth noting that the
presence of right ventricular infarction, as evidenced by ST-segment elevation in the right precordial electrocardiographic leads, is associated with a marked increase in hospital mortality in both younger and older patients (148,149).

Myocardial Rupture

Myocardial rupture is an infrequent complication of acute MI, occurring in less than 5% of patients (150–152). However, when rupture does occur, the course is frequently catastrophic, with death ensuing in over 50% to almost 100% of cases, depending on location. There are three principal types of rupture: ventricular free wall rupture, papillary muscle rupture (PMR), and ventricular septal perforation (acute VSD). PMR almost always occurs following an inferoposterior or posterolateral MI, whereas septal rupture occurs somewhat more frequently following an anterior infarct. Free wall rupture can complicate an infarct of any location.

Although precise figures are unavailable, all forms of rupture appear to occur more frequently in patients over 65 years of age (151,152). Other risk factors for myocardial rupture include female gender and persistent peri-infarctional hypertension (150). Fibrinolytic therapy may also increase the risk of myocardial rupture within the first 24 to 48 hours after treatment, particularly in older patients undergoing delayed fibrinolysis (i.e., more than six hours after symptom onset) (150,152,153).

Impending myocardial rupture is occasionally heralded by persistent vague chest discomfort or unexplained hypotension, but sudden hemodynamic deterioration, new or worsening heart failure, or asystolic cardiac arrest may be the first indication of the rupture (154). The presence of a new systolic murmur, particularly in association with hemodynamic deterioration, strongly suggests the possibility of papillary muscle dysfunction or ventricular septal perforation, and prompt investigation is warranted. Urgent bedside Doppler echocardiography should be performed, since this will enable accurate diagnosis in the majority of cases (155,156). Pulmonary artery catheterization can provide definitive confirmation of a septal perforation by demonstrating an oxygen saturation step up of greater than 10% at the level of the shunt (usually the right ventricle). Similarly, the presence of an abnormally elevated V-wave in the pulmonary capillary wedge pressure waveform suggests acute mitral regurgitation. Cardiac catheterization is usually necessary to define coronary anatomy in elderly patients with cardiac rupture, and left ventriculography can provide diagnostic information on the severity of mitral regurgitation and on the presence and location of an acute VSD.

Once a diagnosis of acute VSD or PMR has been confirmed, supportive measures should be rapidly instituted, and urgent surgical consultation should be obtained (10). Diuretics, an IV inotropic agent, and after-load reduction with IV nitroglycerin or nitroprusside (blood pressure permitting) are appropriate therapy in most cases. Intra-aortic balloon counterpulsation is often effective in stabilizing the patient and should be strongly considered in all surgical candidates (10). Mechanical ventilation is indicated in patients with severe HF or persistent hemodynamic instability.

Surgery is recommended in almost all cases of acute VSD or PMR, since medical therapy is associated with mortality rates of more than 75% (150,157). Perioperative mortality rates range from 10% to 70%, with preoperative left ventricular function and the presence of cardiogenic shock being the most important factors influencing survival (157–159). The long-term prognosis following successful surgical repair of acute VSD or PMR is favorable (157–159).

Rupture of the left ventricular free wall usually progresses rapidly to pericardial tamponade, asystole, and death. Occasionally, however, the rupture will be locally
contained as a result of pericardial adhesions or other factors, resulting in the formation of a pseudoaneurysm. Differentiation of a pseudoaneurysm from a true left ventricular aneurysm can be difficult, but echocardiography, magnetic resonance imaging, and left ventriculography are all useful in making this distinction. The hemodynamic effects of a pseudoaneurysm are variable, depending on its size and location, but there is a tendency for pseudoaneurysms to undergo further rupture, resulting in pericardial tamponade (160,161). Although conservative management may be associated with a favorable outcome in some cases (162), prompt surgical attention is usually recommended once a pseudoaneurysm has been identified (161,163).

Cardiogenic Shock

Cardiogenic shock is defined as the combination of markedly reduced cardiac output (cardiac index < 1.8 L/min/m²), increased left ventricular diastolic pressure or pulmonary wedge pressure (≥22 mmHg), hypotension (systolic blood pressure < 80 mmHg), and tissue hypoperfusion (e.g., prerenal azotemia, impaired sensorium) (164,165). This syndrome occurs twice as frequently in elderly patients with acute MI as in younger subjects, and it accounts for most of the excess mortality associated with acute MI in the elderly (166). Moreover, despite major advances in the treatment of acute MI over the last 30 years, the case fatality rate from cardiogenic shock remains high (166–168).

The causes of cardiogenic shock complicating acute MI are similar to the causes of HF and hypotension. Since few patients survive cardiogenic shock in the absence of a treatable underlying disorder, immediate evaluation for a potentially correctable problem is critical. Emergent Doppler echocardiography should be performed to assess overall left ventricular function and to rule out valvular lesions, pericardial disease, and septal perforation (10). Pulmonary artery catheterization is indicated both to facilitate diagnosis and for guiding therapy (10). Cardiac catheterization may be necessary in some cases if the diagnosis remains in doubt, or as a prelude to PCI or corrective surgery. Although emergent catheterization and coronary revascularization have been shown to improve outcomes in patients up to age 75 with cardiogenic shock complicating acute MI, patients over age 75 may not benefit from these interventions (169).

In patients with a potentially reversible cause of shock, maximally aggressive therapy is indicated to stabilize the patient. In most cases, this will include assisted ventilation, an intra-aortic balloon pump (170), and IV vasoactive therapy. However, when shock is due to irreversible myocardial damage or other untreatable disorder, invasive interventions are unlikely to influence survival and should generally be avoided.

NON-ST-ELEVATION MYOCARDIAL INFARCTION

Non-ST-elevation MI increases in frequency with advancing age and accounts for over 50% of all MIs in patients over the age of 70 (7,9). While ST-elevation MIs are almost always caused by total thrombotic occlusion of the infarct-related vessel (171), the pathogenesis of non-ST-elevation MI is more variable. In the elderly, non-ST-elevation MI may be precipitated by a sustained imbalance between myocardial oxygen supply and demand resulting from severe hypertension, marked hypoxemia due to heart failure or pulmonary embolus, atrial fibrillation with rapid ventricular response, or acute hypotension due to sepsis or other causes. Diffuse, multivessel coronary disease is often present, but total occlusion of the infarct artery is the exception rather than the rule (172,173).
The short-term prognosis following non-ST-elevation MI tends to be better than that following ST-elevation MI, since non-ST-elevation MIs are usually smaller and associated with greater preservation of ventricular function (174). However, patients with non-ST-elevation MI are at increased risk for recurrent ischemia and reinfarction, and long-term survival is similar to that of patients with ST-elevation MI (174,175). In one series, over 60% of all deaths within the first year after hospitalization for acute MI occurred in patients over the age of 70 presenting with non-ST-elevation infarctions (176).

As the clinical course following non-ST-elevation MI is distinct from that following ST-elevation MI, numerous studies have focused specifically on the management of this disorder. In general, the pharmacotherapy of non-ST-elevation MI should include aspirin, LMWH or unfractionated heparin, and a β-blocker (177). Clopidogrel should also be initiated in most cases, especially if PCI is anticipated (9,10,73). A glycoprotein Ib/IIa inhibitor should also be considered in patients likely to undergo early PCI (69,70,177). Nitrates should be administered for persistent or recurrent chest pain or if heart failure is present. In the absence of ST-elevation or left bundle branch block, fibrinolytic therapy has not been shown to be efficacious and should be avoided (19).

Several studies have compared early cardiac catheterization and revascularization with conventional medical therapy in patients with unstable angina or non-ST-elevation MI (178–185). Although the results of these trials have been somewhat inconsistent, on balance the data suggest that early revascularization is beneficial in high-risk patients, including the elderly (9). These findings are reflected in the most recent guidelines for management of non-ST-elevation acute coronary syndromes, which indicate that an invasive approach to therapy is warranted in appropriately selected patients (177). It should be noted, however, that in the Can Rapid Risk Stratification of Unstable Angina Patients Suppress Adverse Outcomes with Early Implementation of the ACC/AHA Guidelines (CRUSADE) quality improvement initiative, an early invasive management strategy did not reduce hospital mortality after adjusting for relevant covariates in a cohort of 5794 patients 75 years of age or older with non-ST-elevation ACS (186). Therefore, caution is warranted in the selection of very elderly patients with non-ST-elevation MI for early catheterization and revascularization (9).

RISK STRATIFICATION

In the past 25 years, the concept of risk stratification has been developed as a means for selecting subgroups of post-MI patients who are most likely to benefit from further diagnostic and therapeutic measures, and conversely, to identify those with a favorable prognosis who are unlikely to benefit from high-cost interventions (187). Factors associated with an increased risk for adverse outcomes include older age, anterior MI location, ischemia occurring either spontaneously or during a post-MI stress test, reduced left ventricular systolic function (especially an ejection fraction less than 40%), frequent premature ventricular contractions or higher grades of ventricular ectopy, reduced heart rate variability (188), increased fibrinogen (189), and elevated C-reactive protein (189,190). Although none of the major risk stratification studies have specifically targeted older patients, key factors identified in younger individuals, particularly left ventricular dysfunction and residual myocardial ischemia, almost certainly retain their prognostic significance in the elderly. In older patients who are suitable candidates for invasive treatment, further risk stratification seems appropriate, and should include an echocardiogram or radionuclide ventriculogram to assess left ventricular function, and an exercise or
pharmacological stress test (e.g., adenosine thallium or dobutamine echocardiogram) to determine the extent of residual ischemia (191–193). On the basis of the results of these investigations, additional intervention may be appropriate, but further study is needed to define the optimal approach to managing high-risk elderly patients.

ETHICAL ISSUES

In general, the foregoing discussion has been predicated on the notion that a given patient is an “appropriate” or “suitable” candidate for each intervention under consideration. These terms, while vague, imply that not all patients should receive every intervention, and that multiple factors must be taken into consideration during the decision-making process. Among these are the wishes of the patient, as expressed either directly or through a prior communication such as a living will; the anticipated impact of the intervention on quality of life and long-term prognosis; the potential for the intervention itself to add to the patient’s suffering; and the concerns of the patient’s family and friends.

The physician’s role in guiding these decisions is critically important, and a high level of compassion, honesty, and respect for the patient’s autonomy is required. Thus, the physician must provide a balanced view of the available therapeutic options, including a realistic appraisal of the likelihood of various outcomes and adverse events. The physician should avoid creating an overly grim picture, but at the same time must avoid fostering unrealistic hopes. Finally, when the patient’s condition is such that death seems inevitable, the physician must be able to provide appropriate counsel to forego or withdraw interventions that are unlikely to be helpful, and which will only serve to prolong the dying process. In addition, the physician must provide comfort and emotional support for the patient and family. In this regard, the importance of the nursing staff, members of the clergy, and other health professionals in helping the patient and family deal with emotional issues and other concerns cannot be overemphasized.

SUMMARY

Acute myocardial infarction occurs at increasing frequency with advancing age, and older patients with acute MI are at increased risk for major complications, including HF, arrhythmias and conduction disturbances, myocardial rupture, cardiogenic shock, and death. Older patients thus comprise a large high-risk subgroup of the MI population who may derive substantial benefits from appropriately selected therapeutic interventions. At the same time, many interventions are associated with increased risk in the elderly, so that individualization of treatment is essential. Optimal therapy is thus based on a careful risk–benefit assessment of the available treatment options in conjunction with appropriate consideration of patient preferences and other relevant factors.

Although many therapeutic trials in acute MI patients have either excluded elderly patients or enrolled too few older subjects to permit definitive conclusions, sufficient data are available to make specific recommendations in several areas. As shown in Table 4, aspirin, LMWH, fibrinolytic agents, and primary PCI are of proven value during the acute phase of MI in selected elderly patients. Early initiation of β-blockers, ACE inhibitors, and statins is also likely to be beneficial. Following MI, aspirin, β-blockers, ACE inhibitors, and statins are of proven benefit and should be considered standard therapy in most patients. Selected patients may also benefit from clopidogrel, warfarin, percutaneous or surgical revascularization, or implantation of an ICD. Conversely, routine use of calcium channel blockers and antiarrhythmic agents is not recommended.
As the age of the population continues to increase, the number of older patients at risk for acute MI will rise commensurately. Although progressively more sophisticated interventions may result in sizable reductions in post-MI morbidity and mortality, it is apparent, given the high risk of adverse outcomes in the elderly population, that the best treatment is prevention. Thus, the greatest potential for the future, as well as the greatest challenge, will be to develop more effective strategies for preventing atherosclerosis and for conquering the epidemic of coronary heart disease in our aging population.

Table 4  Efficacy of Selected Treatments for Acute Myocardial Infarction in Elderly Patients

<table>
<thead>
<tr>
<th>Effective</th>
<th>Probably effective</th>
<th>Uncertain efficacy</th>
<th>Ineffective</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Acute phase</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Aspirin</td>
<td>Intravenous heparin</td>
<td>Nitrates</td>
<td>Calcium antagonists</td>
</tr>
<tr>
<td>LMWH</td>
<td>β-Blockers</td>
<td></td>
<td></td>
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<tr>
<td>Fibrinolysis</td>
<td>ACE inhibitors</td>
<td>Antiarrhythmic agents</td>
<td></td>
</tr>
<tr>
<td>Primary PCI</td>
<td>Glycoprotein IIb/IIIa inhibitors</td>
<td>Magnesium</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Statins</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Chronic phase</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Aspirin</td>
<td>Clopidogrel</td>
<td>Antiarrhythmic agents</td>
<td></td>
</tr>
<tr>
<td>β-Blockers</td>
<td>Warfarin</td>
<td></td>
<td></td>
</tr>
<tr>
<td>ACE inhibitors</td>
<td>PCI</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Statins</td>
<td>Coronary surgery</td>
<td>Calcium channel blockers</td>
<td></td>
</tr>
<tr>
<td></td>
<td>ICDs</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*Selected subgroups; see text.

Abbreviations: ACE, angiotensin-converting enzyme; ICDs, implantable cardioverter-defibrillators; LMWH, low-molecular-weight heparin; PCI, percutaneous coronary intervention.

As the age of the population continues to increase, the number of older patients at risk for acute MI will rise commensurately. Although progressively more sophisticated interventions may result in sizable reductions in post-MI morbidity and mortality, it is apparent, given the high risk of adverse outcomes in the elderly population, that the best treatment is prevention. Thus, the greatest potential for the future, as well as the greatest challenge, will be to develop more effective strategies for preventing atherosclerosis and for conquering the epidemic of coronary heart disease in our aging population.

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Therapy of Acute Myocardial Infarction

12
Management of the Older Patient After Myocardial Infarction

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INTRODUCTION

Coronary artery disease (CAD) is the leading cause of death in older persons. Although persons older than 65 years comprise 12% of the population (1), approximately 60% of hospital admissions for acute myocardial infarction (MI) occur in persons older than 65 years of age, and persons older than 75 years of age account for nearly half of these admissions of patients with MI older than 65 years (2). Not only is the in-hospital mortality higher in older patients with MI than in younger patients with MI, but the postdischarge mortality rate is also higher in older persons, with the one-year cardiac mortality rate of 12% in patients aged 65 to 75 years and 17.6% in patients older than 75 years (3). Approximately two-thirds of these one-year deaths were sudden or related to a new MI (3). This chapter discusses the management of the older patient after MI.

CONTROL OF CORONARY RISK FACTORS

Cigarette Smoking

The Chicago Stroke Study demonstrated that current cigarette smokers 65 to 74 years of age had a 52% higher mortality from CAD than nonsmokers, ex-smokers, and pipe and cigar smokers (4). Ex-smokers who had stopped smoking for one to five years had a similar mortality from CAD, as did nonsmokers (4). The Systolic Hypertension in the Elderly Program pilot project showed that smoking was a predictor of first cardiovascular event and MI/sudden death (5). At 30-year follow-up of persons 65 years of age and older in the Framingham Study, cigarette smoking was not associated with the incidence of CAD in older men and women but was associated with mortality from CAD in them (6).

At 12-year follow-up of men aged 65 to 74 years in the Honolulu Heart Program, cigarette smoking was an independent risk factor for nonfatal MI and fatal CAD (7). The absolute excess risk associated with cigarette smoking was 1.9 times higher in older men than in middle-aged men. At five-year follow-up in three communities of 7178 persons 65 years of age or older, current cigarette smokers had a higher incidence of cardiovascular
mortality than nonsmokers (relative risk = 2 for men and 1.6 for women) (8). The incidence of cardiovascular death in former smokers was similar to those who had never smoked (8). At six-year follow-up of older men and women in the Coronary Artery Surgery Study registry, the relative risk of MI or death was 1.5 for persons aged 65 to 69 years and 2.9 for persons 70 years or older who continued smoking compared with quitters during the year before study enrollment (9).

At 40-month follow-up of 664 men of mean age 80 years, and at 48-month follow-up of 1488 women of mean age 82 years, current cigarette smoking increased the relative risk of new coronary events (nonfatal or fatal MI or sudden cardiac death) 2.2 times in older men and 2.0 times in older women (Table 1) (10). We have also observed that cigarette smoking aggravates angina pectoris and precipitates silent myocardial ischemia in older persons with CAD.

On the basis of the available data, older persons who smoke should be strongly encouraged to stop smoking because it will reduce cardiovascular mortality and all-cause mortality after MI. A smoking cessation program should be recommended.

### Hypertension

Increased peripheral vascular resistance is the cause of systolic and diastolic hypertension in older persons. Systolic hypertension in older persons is diagnosed if the systolic blood pressure is 140 mmHg or higher on three occasions (11,12). Diastolic hypertension in older persons is diagnosed if the diastolic blood pressure is 90 mmHg or higher on three occasions (1,12). Isolated systolic hypertension in older persons is diagnosed if the systolic blood pressure is 140 mmHg or higher on three occasions, and the diastolic blood pressure is normal (11,12). In a study, isolated systolic hypertension was observed in 51% of 499 older persons with hypertension (12).

Isolated systolic hypertension and diastolic hypertension are both associated with increased cardiovascular morbidity and mortality in older persons (13). Increased systolic blood pressure is a greater risk factor for cardiovascular morbidity and mortality than

### Table 1  Risk Factors for New Coronary Events in 664 Older Men and in 1488 Older Women

<table>
<thead>
<tr>
<th>Risk factor</th>
<th>Relative risk of new coronary events</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>1.04</td>
</tr>
<tr>
<td>Prior coronary artery disease</td>
<td>1.7</td>
</tr>
<tr>
<td>Cigarette smoking</td>
<td>2.2</td>
</tr>
<tr>
<td>Hypertension</td>
<td>2.0</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>1.9</td>
</tr>
<tr>
<td>Obesity</td>
<td>NS</td>
</tr>
<tr>
<td>Serum total cholesterol</td>
<td>1.12a</td>
</tr>
<tr>
<td>Serum HDL cholesterol</td>
<td>1.70b</td>
</tr>
<tr>
<td>Serum triglycerides</td>
<td>NS</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Risk factor</th>
<th>Relative risk of new coronary events</th>
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<tbody>
<tr>
<td>Age</td>
<td>1.03</td>
</tr>
<tr>
<td>Prior coronary artery disease</td>
<td>1.9</td>
</tr>
<tr>
<td>Cigarette smoking</td>
<td>2.0</td>
</tr>
<tr>
<td>Hypertension</td>
<td>1.6</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>1.8</td>
</tr>
<tr>
<td>Obesity</td>
<td>NS</td>
</tr>
<tr>
<td>Serum total cholesterol</td>
<td>1.12a</td>
</tr>
<tr>
<td>Serum HDL cholesterol</td>
<td>1.12a</td>
</tr>
<tr>
<td>Serum triglycerides</td>
<td>1.002</td>
</tr>
</tbody>
</table>

a1.12 times higher probability of developing new coronary events for an increment of 10 mg/dL of serum total cholesterol.

b1.70 times higher probability of developing new coronary events for a decrement of 10 mg/dL of serum HDL cholesterol.

c1.95 times higher probability of developing new coronary events for a decrement of 10 mg/dL of serum HDL cholesterol.

**Abbreviations:** NS, not significant by multivariate analysis; HDL, high-density lipoprotein.

**Source:** From Ref. 10.
increased diastolic blood pressure (13). The higher the systolic or diastolic blood pressure, the greater the morbidity and mortality from CAD in older men and women.

At 30-year follow-up of persons aged 65 years and older in the Framingham Study, systolic hypertension correlated with the incidence of CAD in older men and women (6). Diastolic hypertension correlated with CAD in older men but not in older women (6). At 40-month follow-up of older men and 48-month follow-up of older women, systolic or diastolic hypertension increased the relative risk of new coronary events 2.0 times in men and 1.6 times in women (Table 1) (10).

Older persons with hypertension should be treated initially with salt restriction, weight reduction if necessary, cessation of drugs that increase blood pressure, avoidance of alcohol and tobacco, increase in physical activity, reduction of dietary saturated fat and cholesterol, and maintenance of adequate dietary potassium, calcium, and magnesium intake.

Antihypertensive drugs have been demonstrated to decrease new coronary events in older men and women with hypertension (Table 2) (14–18). The Joint National Committee (JNC) on Detection, Evaluation, and Treatment of High Blood Pressure recommends as initial drug therapy diuretics or β blockers because these drugs have been shown to reduce cardiovascular morbidity and mortality in controlled clinical trials (11). Persons with prior MI should be treated with β blockers and angiotensin-converting enzyme (ACE) inhibitors and not treated with calcium channel blockers or α blockers (11,19–26). JNC VII also recommends use of aldosterone antagonists in the treatment of hypertension after MI on the basis of the EPHESUS trial (11,27). Patients treated with aldosterone antagonists should not have significant renal dysfunction or hyperkalemia (19). In an observational prospective study 1212 men and women, mean age 80 years, with prior MI and hypertension were treated with β blockers, ACE inhibitors, diuretics, calcium channel blockers, or α blockers; at 40-month follow-up, the incidence of new coronary events in persons treated with one antihypertensive drug was lowest in persons treated with β blockers or ACE inhibitors (26). In older persons treated with two antihypertensive drugs, the incidence of new coronary events was lowest in persons treated with β blockers plus ACE inhibitors (26).

The benefit of β blockers in reducing coronary events in older persons with prior MI is especially increased in persons with diabetes mellitus (22), symptomatic peripheral
arterial disease (23), abnormal left ventricular ejection fraction (LVEF) (21,28), complex ventricular arrhythmias with abnormal LVEF (29) or normal LVEF (30), and with congestive heart failure (CHF) with abnormal LVEF (31) or normal LVEF (32). β Blockers should also be used to treat older persons with hypertension who have angina pectoris (33), myocardial ischemia (34), supraventricular tachyarrhythmias such as atrial fibrillation with a rapid ventricular rate (35), hyperthyroidism (36), preoperative hypertension (11), migraine (11), or essential tremor (11).

In addition to β blockers, older persons with hypertension and CHF should be treated with diuretics and ACE inhibitors or angiotensin receptor blockers (ARBs) and patients with persistent severe symptoms with aldosterone antagonists (11,27,37,38). ACE inhibitors or ARBs should also be administered to persons with diabetes mellitus, renal insufficiency, or proteinuria (11,39). The blood pressure should be lowered to less than 140/90 mmHg after MI, to less than 130/80 mmHg in persons with diabetes mellitus or renal insufficiency, and preferably to less than 120/80 mmHg (11,19).

Dyslipidemia

**Serum Total Cholesterol**

In the Framingham Study, serum total cholesterol was an independent risk factor for CAD in older men and women (40). Among patients aged 65 years or older with prior MI in the Framingham Study, serum total cholesterol was most strongly related to death from CAD and to all-cause mortality (41). Many other studies have documented that a high serum total cholesterol is a risk factor for new coronary events in older men and women (5,10,42–44).

During nine-year follow-up of 350 men and women, mean age 79 years, in the Bronx Aging Study, a consistently increased serum low-density lipoprotein (LDL) cholesterol was associated with the development of MI in older women (45). In the Established Populations for Epidemiologic Studies of the Elderly (EPESE) project, serum total cholesterol was a risk factor for mortality from CAD in older women but not in older men (46). At 40-month follow-up of older men and 48-month follow-up of older women, an increment of 10 mg/dL of serum total cholesterol increased the relative risk of new coronary events by 1.12 times in both men and women (Table 1) (10).

**Serum High-Density Lipoprotein Cholesterol**

A low serum high-density lipoprotein (HDL) cholesterol is a risk factor for new coronary events in older men and women (5,10,40,45–48). In the Framingham Study (40), EPESE (46), and in our study (10), a low serum HDL cholesterol was a more powerful predictor of new coronary events than was serum total cholesterol.

During nine-year follow-up of 350 men and women in the Bronx Aging Study, a consistently low serum HDL cholesterol level was independently associated with the development of MI, cardiovascular disease, or death in men (45). At 40-month follow-up of 664 older men and 48-month follow-up of 1488 older women, multivariate analysis showed that there was a 1.70 times higher probability of developing new coronary events in men and a 1.95 times higher probability of developing new coronary events in women for a decrement of 10 mg/dL of serum HDL cholesterol (Table 1) (10).

**Serum Triglycerides**

Hypertriglyceridemia has been reported to be a risk factor for new coronary events in older women but not in older men (10,40). At 40-month follow-up of older men and at
Management of the Older Patient After Myocardial Infarction

48-month follow-up of older women, multivariate analysis demonstrated that serum triglycerides was not a risk factor for new coronary events in older men and was a very weak risk factor for new coronary events in older women (Table 1) (10).

Drug Therapy of Hypercholesterolemia

At 5.4-year median follow-up of 4444 men and women (1021 aged 65–70 years) with CAD and hypercholesterolemia in the Scandinavian Simvastatin Survival Study, compared with placebo, simvastatin 20 to 40 mg daily significantly decreased in patients aged 65 to 70 years total mortality by 34%, CAD mortality by 43%, major coronary events by 34%, nonfatal MI by 33%, any acute CAD-related endpoint by 33%, any atherosclerosis-related endpoint by 34%, and coronary revascularization procedures by 41% (Table 3) (49). The absolute risk reduction for both all-cause mortality and CAD mortality was approximately twice as great in persons 65 to 70 years of age at study entry as in those younger than 65 years (49).

Table 3 Effects of Lowering Increased Serum Total Cholesterol and Low-Density Lipoprotein Cholesterol Levels by Simvastatin and Pravastatin Vs. Placebo in Older Patients with CAD

<table>
<thead>
<tr>
<th>Study (Ref.)</th>
<th>Follow-up</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Scandinavian Simvastatin Survival Study (49) (4444 men and women, 1021 aged 65 to 70 yr, with CAD and hypercholesterolemia)</td>
<td>5.4 yr</td>
<td>In patients ≥65 yr, compared with placebo, simvastatin decreased all-cause mortality by 34%, CAD mortality by 43%, major coronary events by 34%, nonfatal MI by 33%, any acute CAD-related event by 33%, any atherosclerosis-related endpoint by 34%, and coronary revascularization procedures by 41%.</td>
</tr>
<tr>
<td>Cholesterol and Recurrent Events Trial (50) (4159 men and women, 1283 aged 65–75 yr, with MI and serum total cholesterol &lt;240 mg/dL but serum LDL cholesterol ≥115 mg/dL)</td>
<td>5.0 yr</td>
<td>Compared with placebo, pravastatin decreased CAD death by 45%, CAD death or nonfatal MI by 39%, major coronary events by 32%, coronary revascularization by 32%, stroke by 40%, and insignificantly decreased unstable angina by 8%, and congestive heart failure by 23%.</td>
</tr>
<tr>
<td>Long-Term Intervention with Pravastatin in Ischaemic Disease Study (51) (9014 men and women, 3514 aged 65–75 yr, with MI or unstable angina and mean serum total cholesterol 218 mg/dL).</td>
<td>6.1 yr</td>
<td>Compared with placebo, pravastatin reduced all-cause mortality by 22%, death from CAD by 24%, fatal and nonfatal MI by 29%, death from cardiovascular disease by 25%, need for coronary artery surgery by 22%, need for coronary angioplasty by 19%, hospitalization for unstable angina by 12%, and stroke by 19%.</td>
</tr>
<tr>
<td>Heart Protection Study (52) (20,536 men and women, 10,697 aged 65–85 yr, with CAD, occlusive arterial disease of noncoronary arteries, diabetes, or treated hypertension and no serum lipid requirement)</td>
<td>5.0 yr</td>
<td>Compared with placebo, simvastatin reduced all-cause mortality by 13%, any vascular mortality by 17%, major coronary events by 27%, any stroke by 25%, any revascularization procedure by 24%, and any major vascular event by 24%.</td>
</tr>
</tbody>
</table>

Abbreviations: CAD, coronary artery disease; MI, myocardial infarction; LDL, low-density lipoprotein
At five-year follow-up of 4159 men and women (1283 aged 65–75 years) with MI and serum total cholesterol levels below 240 mg/dL but serum LDL cholesterol levels greater than or equal to 115 mg/dL in the Cholesterol and Recurrent Events trial, compared with placebo, administration of pravastatin 40 mg daily significantly reduced in patients aged 65 to 75 years CAD death by 45%, CAD death or nonfatal MI by 39%, major coronary events by 32%, coronary revascularization by 32%, and insignificantly reduced unstable angina pectoris by 8% and CHF by 23% (Table 3) (50). For every 1000 patients 65 years and older treated for five years with pravastatin, 225 cardiovascular hospitalizations would be prevented compared with the prevention of 121 cardiovascular hospitalizations in 1000 patients younger than 65 years (50).

At 6.1-year mean follow-up of 9014 men and women (3514 of whom were aged 65–75) with MI (64%) or unstable angina pectoris (36%) and serum total cholesterol levels of 155 to 271 mg/dL in the Long-Term Intervention with Pravastatin in Ischaemic Disease Study, compared with placebo, pravastatin 40 mg daily significantly reduced all-cause mortality by 22%, death from CAD by 24%, fatal and nonfatal MI by 29%, death from cardiovascular disease by 25%, need for coronary artery bypass surgery by 22%, need for coronary angioplasty by 19%, hospitalization for unstable angina pectoris by 12%, and stroke by 19% (Table 3) (51). The absolute benefits of treatment with pravastatin were greater in groups of persons at higher absolute risk for a major coronary event such as older persons, those with a higher serum LDL cholesterol level, those with a lower serum HDL cholesterol level, and those with a history of diabetes mellitus or smoking (51).

At five-year follow-up of 20,536 British men and women (10,697 of whom were aged 65–80 years) with either CAD, occlusive arterial disease of noncoronary arteries, diabetes mellitus, or treated hypertension and no serum lipid requirement in the Heart Protection Study, compared with placebo, simvastatin 40 mg daily significantly reduced all-cause mortality by 13%, any vascular mortality by 17%, major coronary events by 27%, any stroke by 25%, any revascularization procedure by 24%, and any major vascular event by 24% (Table 3) (52). In the 1263 persons aged 75 to 80 years at study entry and 80 to 85 years at follow-up, any major vascular event was significantly reduced 28% by simvastatin. Lowering serum LDL cholesterol from less than 116 mg/dL to less than 77 mg/dL by simvastatin caused a 25% significant reduction in vascular events (52).

In the Heart Protection Study, 3500 persons had initial serum LDL cholesterol levels less than 100 mg/dL (52). Decrease of serum LDL cholesterol from 97 mg/dL to 65 mg/dL by simvastatin in these persons caused a similar decrease in risk as did treating patients with higher serum LDL cholesterol levels. The Heart Protection Study investigators recommended treating persons at high risk for cardiovascular events with statins, regardless of the initial levels of serum lipids, age, or gender (52).

On the basis of these and other data (53–56) the American College of Cardiology/American Heart Association (ACC/AHA) guidelines (19) and the updated National Cholesterol Education Program III guidelines (57) state that in very high-risk persons, a serum LDL cholesterol level of less than 70 mg/dL is a reasonable clinical strategy. When a high-risk person has hypertriglyceridemia or low HDL cholesterol, consideration can be given to combining a fibrate or nicotinic acid with an LDL-cholesterol-lowering drug. (19,57).

**Diabetes Mellitus**

Diabetes mellitus is a risk factor for new coronary events in older men and women (10,58). At 40-month follow-up of older men and 48-month follow-up of older women, diabetes mellitus was found by multivariate analysis to increase the relative risk of new coronary events 1.9 times in men and 1.8 times in women (Table 1) (10).
Diabetic patients are more often obese and have higher serum LDL cholesterol and triglycerides levels and lower serum HDL cholesterol levels than do nondiabetics. Diabetics also have a higher prevalence of hypertension and left ventricular hypertrophy than do nondiabetics. These risk factors contribute to the higher incidence of new coronary events in diabetics than in nondiabetics. Diabetics with microalbuminuria have more severe angiographic CAD than diabetics without microalbuminuria (59). Diabetics also have a significant increasing trend of hemoglobin A1c levels over the increasing number of vessels with CAD (60).

Older diabetics after MI should be treated with dietary therapy, weight reduction therapy if necessary, and appropriate drugs if needed to control hyperglycemia. Other coronary risk factors such as smoking, hypertension, dyslipidemia, obesity, and physical inactivity should be controlled. The blood pressure should be lowered to less than 130/80 mmHg by an ACE inhibitor or by an ARB (11,19,20,39,61). The serum LDL cholesterol level should be reduced to less than 70 mg/dL (19,57). As data showed an increased incidence of coronary events and of mortality in diabetics with CAD treated with sulfonylureas (62–64), these drugs should be avoided if possible in postinfarction patients with diabetes mellitus. The hemoglobin A1c level should be reduced to less than 7% in patients with diabetes mellitus (19).

Obesity

In the Framingham Study, obesity was an independent risk factor for new coronary events in older men and women (58). Disproportionate distribution of fat to the abdomen assessed by the waist-to-hip circumference ratio has also found to be a risk factor for cardiovascular disease, mortality from CAD, and total mortality in older men and women (65,66). At 40-month follow-up of older men and 48-month follow-up of older women, obesity was a risk factor for new coronary events in men and women by univariate analysis but not by multivariate analysis (Table 1) (10).

Obese patients who have had a MI must undergo weight reduction (19). Weight reduction is also the first approach to controlling hyperglycemia, mild hypertension, and dyslipidemia before placing persons on long-term drug therapy. Regular aerobic exercise should be advised with proper diet in treating obesity. The body mass index should be reduced to a level between 18.5 and 24.9 kg/m² (19).

Physical Inactivity

Physical inactivity is associated with obesity, dyslipidemia, hyperglycemia, and hypertension. At 12-year follow-up in the Honolulu Heart Program, physically active men aged 65 years or older had a relative risk of 0.43 for CAD compared with inactive men (67). Exercise training programs are not only beneficial in preventing CAD (68) but have also been shown to improve endurance and functional capacity in older persons after MI (69,70). The goal to be achieved is at least 30 minutes of exercise daily for seven days per week with a minimum of five days of physical exercise per week (19).

ASPIRIN

Aspirin decreases the aggregation of platelets exposed to thrombogenic stimuli by inhibiting the cyclooxygenase enzyme reaction within the platelet and, thereby, blocking synthesis of thromboxane A₂, a powerful stimulus to platelet aggregation and vasoconstriction (71).
Randomized trials involving 20,006 patients showed that aspirin and other antiplatelet drugs administered to patients after MI decreased the incidence of recurrent MI, stroke, or vascular death by 36 events per 1000 patients treated for two years (72). The benefit of aspirin in decreasing MI, stroke, or vascular death in patients after MI was irrespective of age, sex, blood pressure, and diabetes mellitus (72).

Data from the Multicenter Study of Myocardial Ischemia in 936 patients enrolled one to six months after an acute MI (70% of patients) or unstable angina pectoris (30% of patients) showed at 23-month follow-up that the cardiac mortality rate was 1.6% for aspirin users and 5.4% for nonusers of aspirin (73). Cardiac mortality was reduced by 90% in aspirin users who underwent thrombolytic therapy compared with nonusers of aspirin who underwent thrombolytic therapy (73).

The Coumadin Aspirin Reinfarction Study (CARS) randomized 8803 low-risk patients after MI to aspirin 160 mg daily, aspirin 80 mg plus warfarin 1 mg daily, or to aspirin 80 mg plus warfarin 3 mg daily (74). At follow-up, the combined incidence of cardiovascular death, recurrent MI, and stroke was similar in all the three treatment groups (74). The incidence of mortality was also similar in these three treatment groups. However, the incidence of nonfatal stroke was reduced by aspirin 160 mg daily (74). Data from the Combination Hemotherapy and Mortality and Prevention Study showed in 5059 postinfarction patients that warfarin administered in a dose to achieve an international normalized ratio (INR) of 1.8 combined with low-dose aspirin did not provide a clinical benefit beyond that achieved with aspirin alone (75).

Of 5490 survivors of acute MI aged 65 years or older, with no contraindications to aspirin, 4149 patients (76%) received aspirin at the time of hospital discharge (76). At the six-month follow-up evaluation, aspirin users had a significant 23% reduction in mortality (76).

In an observational prospective study of 1410 patients, mean age 81 years, with prior MI and a serum LDL cholesterol of 125 mg/dL or higher, 832 patients (59%) were treated with aspirin (77). At three-year follow-up, use of aspirin caused a 52% significant independent reduction in new coronary events (95% CI, 0.41–0.55) (77). Use of statins caused a 54% significant independent reduction in the incidence of new coronary events (95% CI, 0.40–0.53) (77).

On the basis of the available data, all patients should receive aspirin in a dose of 160 to 325 mg daily on day 1 of an acute MI and continue aspirin in a dose of 75 to 162 mg daily for an indefinite period unless there is a specific contraindication to its use (19,78).

Clopidogrel is also an excellent antiplatelet drug that is effective in reducing MI, ischemic stroke, and vascular death in postinfarction patients (79). The ACC/AHA guidelines recommend the use of clopidogrel in postinfarction patients who cannot tolerate aspirin for an indefinite period unless there is a specific contraindication to its use (19,78).

### ANTICOAGULANTS

The routine use of warfarin after MI is controversial (80). However, three well-controlled studies have shown a reduction in mortality and/or morbidity in patients receiving long-term oral anticoagulation therapy after MI (81–83). The Sixty Plus Reinfarction Study Group reported at two-year follow-up after MI of patients, mean age 68 years, that compared with placebo,acenocoumarin or phenprocoumon caused a 26% nonsignificant decrease in mortality, a 55% significant reduction in recurrent MI, and a 40% nonsignificant decrease in stroke (81). The Warfarin Reinfarction Study Group showed at 37-month follow-up after MI of patients 75 years of age or younger that compared with
placebo, warfarin caused significant reductions in mortality (24%), recurrent MI (34%), and stroke (55%) (82). The Anticoagulation in the Secondary Prevention of Events in Coronary Thrombosis Research Group reported at 37-month follow-up after MI of patients, mean age 61 years, that compared with placebo, nicoumalone or phenprocoumon caused a 10% nonsignificant decrease in mortality, a 53% significant reduction in recurrent MI, and a 42% significant decrease in stroke (83).

The ACC/AHA guidelines recommend as class I indications for long-term oral anticoagulant therapy after MI (i) secondary prevention of MI in post-MI patients unable to tolerate daily aspirin or clopidogrel, (ii) in post-MI patients with persistent atrial fibrillation, and (iii) post-MI patients with left ventricular thrombus (19,78). Long-term warfarin should be administered in a dose to achieve an INR between 2 and 3 (19,78).

**β BLOCKERS**

β Blockers are very effective antianginal and anti-ischemic agents and should be administered to all patients with angina pectoris or silent myocardial ischemia due to CAD unless there are specific contraindications to their use (33). Teo et al. (84) analyzed 55 randomized controlled trials comprising 53,268 patients that investigated the use of β blockers after MI. β Blockers significantly decreased mortality by 19% in these studies (84). A randomized, double-blind, placebo-controlled study of propranolol in high-risk survivors of acute MI at 12 Norwegian hospitals showed a 52% reduction in sudden cardiac death in persons treated with propranolol for one year (85).

Table 4 shows that metoprolol (86), timolol (87,88), and propranolol (89) caused a greater decrease in mortality after MI in older persons than in younger persons. The reduction in mortality after MI in patients treated with β blockers was due to both a reduction in sudden cardiac death and recurrent MI (87–89). In persons with an LVEF less than or equal to 40% after MI, compared with placebo, persons aged 25 to 90 years randomized to carvedilol had a 23% significant reduction in mortality at 1.3-year follow-up (90). A retrospective cohort study also showed that MI patients aged 60 to 89 years treated with metoprolol had an age-adjusted mortality decrease of 76% (91).

In the Beta Blocker Heart Attack Trial, propranolol caused a 27% decrease in mortality in patients with a history of CHF and a 25% decrease in mortality in patients without CHF (92). In this study, propranolol caused a 47% reduction in sudden cardiac death in patients with a history of CHF and a 13% reduction in sudden cardiac death in patients without CHF (92).

In the Beta-Blocker Pooling Project, results from nine studies involving 3519 patients with CHF at the time of acute MI demonstrated that β blockers caused a 25% decrease in mortality (93). In the Multicenter Diltiazem Postinfarction Trial, the 2.5-year risk of total mortality in patients with an LVEF, less than 30% was 24% for patients receiving β blockers (relative risk = 0.53) versus 45% for patients not receiving β blockers (94). β Blockers have also been found to reduce mortality in patients with CAD and CHF associated with an LVEF less than or equal to 35% (31,95–97) or greater than or equal to 40% (32,97).

An observational prospective study was performed in 477 patients, mean age 79 years, with prior MI and an LVEF less than 40% (mean LVEF 31%) (21). At 34-month follow-up, patients treated with β blockers without ACE inhibitors had a 25% significant reduction in new coronary events and a 41% significant reduction in CHF (21). At 41-month follow-up, patients treated with both β blockers and ACE inhibitors had a significant 37% reduction in new coronary events and a significant 60% reduction in CHF (21).
A retrospective analysis of the use of β blockers after MI in a New Jersey Medicare population from 1987 to 1992 showed that only 21% of older persons after MI without contraindications to β blockers were treated with β blockers (98). Older patients, who were treated with β blockers after MI, had a 43% decrease in two-year mortality and a 22% decrease in two-year cardiac hospital readmissions compared with older patients who were not treated with β blockers (98). Use of a calcium channel blocker instead of a β blocker after MI doubled the risk of mortality (98).

β Blockers have also been demonstrated to reduce mortality in older patients with complex ventricular arrhythmias after MI and an LVEF greater than or equal to 40% (30) or less than or equal to 40% (29). The decrease in mortality in older patients with heart disease and complex ventricular arrhythmias caused by propranolol is more because of an anti-ischemic effect than to an antiarrhythmic effect (34). In these patients, propranolol also markedly decreased the circadian variation of ventricular arrhythmias (99), abolished the circadian variation of myocardial ischemia (100), and abolished the circadian variation of sudden cardiac death or fatal MI (101).

A meta-analysis of trials also showed that the use of β blockers after non-Q-wave MI is likely to reduce mortality and recurrent MI by 25% (102). Therefore, older patients with Q-wave MI or non-Q-wave MI without contraindications to β blockers should be treated with β blockers for at least six years after MI. β Blockers with intrinsic sympathomimetic activity should not be used. The ACC/AHA guidelines recommend that patients without a clear contraindication to β-blocker therapy should receive β blockers within a few days of MI (if not initiated acutely) and continue them indefinitely (19,78).

### Table 4  Effect of β Blockers on Mortality After Myocardial Infarction

<table>
<thead>
<tr>
<th>Study (Ref.)</th>
<th>Follow-up</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Goteborg Trial (86)</td>
<td>90 days</td>
<td>Compared with placebo, metoprolol caused a 21% nonsignificant decrease in mortality in patients &lt;65 yr and a 45% significant decrease in mortality in patients 65–74 yr.</td>
</tr>
<tr>
<td>Norwegian Multicenter Study</td>
<td>17 mo (up to 33 mo)</td>
<td>Compared with placebo, timolol caused a 31% significant reduction in mortality in persons &lt;65 yr and a 43% significant reduction in mortality in persons 65–74 yr.</td>
</tr>
<tr>
<td>Norwegian Multicenter Study</td>
<td>61 mo (up to 72 mo)</td>
<td>Compared to placebo, timolol caused a 13% nonsignificant decrease in mortality in persons &lt;65 yr and a 19% significant decrease in mortality in persons 65–74 yr.</td>
</tr>
<tr>
<td>Beta Blocker Heart Attack Trial</td>
<td>25 mo (up to 36 mo)</td>
<td>Compared with placebo, propranolol caused a 19% nonsignificant reduction in mortality in persons &lt;60 yr and a 33% significant reduction in mortality in persons 60–69 yr.</td>
</tr>
<tr>
<td>CAPRICORN Trial (90)</td>
<td>1.3 yr</td>
<td>In patients, mean age 63 yr (range 25–90 yr) with a left ventricular ejection fraction ≤40% after MI, compared with placebo, carvedilol caused a 23% significant reduction in mortality.</td>
</tr>
</tbody>
</table>

**Abbreviations:** CAPRICORN, Carvedilol Post-Infarct Survival Control in Left Ventricular Dysfunction; MI, myocardial infarction.
NITRATES

Long-acting nitrates are effective antianginal and anti-ischemic drugs (103). These drugs should be administered along with β blockers to patients after MI who have angina pectoris. The dose of oral isosorbide dinitrate prescribed should be gradually increased to a dose of 30 to 40 mg administered thrice daily if tolerated. Isosorbide-5-mononitrate in a dose of 60 mg may also be administered once daily. To avoid nitrate tolerance, there should be a nitrate-free interval of 12 hours each day (104). β Blockers should be used to prevent angina pectoris and rebound myocardial ischemia during the nitrate-free interval.

ACE INHIBITORS

ACE inhibitors improve symptoms, quality of life, and exercise tolerance in patients with CHF and an abnormal LVEF (105) or a normal LVEF (106). An overview of 32 randomized trials comprising 7105 patients with CHF showed that ACE inhibitors reduced mortality by 23% and mortality or hospitalization for CHF by 35% (107). Patients who develop CHF after MI should be treated with ACE inhibitors unless there are specific contraindications to their use.

Table 5 shows that ACE inhibitors reduce mortality in patients after MI (20,108–112). In the Survival and Ventricular Enlargement Trial, asymptomatic patients with an LVEF less than or equal to 40% treated with captopril 3 to 16 days after MI had, at 42-month follow-up compared with placebo, a 19% reduction in mortality, a 21% reduction in mortality or hospitalization for CHF, and a 13% reduction in the combined endpoint of cardiovascular death or MI (108).

<table>
<thead>
<tr>
<th>Study (Ref.)</th>
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<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Survival and Ventricular Enlargement Trial (108)</td>
<td>42 mo (up to 60 mo)</td>
<td>In patients with MI and LVEF ≤40%, compared with placebo, captopril reduced mortality 8% in patients aged ≤55 yr, 13% in patients aged 56 to 64 yr, and 25% in patients aged ≥65 yr.</td>
</tr>
<tr>
<td>Acute Infarction Ramipril Efficacy Study (109)</td>
<td>15 mo</td>
<td>In patients with MI and clinical evidence of CHF, compared with placebo, ramipril decreased mortality 2% in patients aged &lt;65 yr and 36% in patients aged ≥5 yr.</td>
</tr>
<tr>
<td>Survival of Myocardial Infarction Long-Term Evaluation Trial (110)</td>
<td>1 yr</td>
<td>In patients with anterior MI, compared with placebo, zofenopril reduced mortality or severe CHF 32% in patients aged &lt;65 yr and 39% in patients aged ≥65 yr.</td>
</tr>
<tr>
<td>Trandolapril Cardiac Evaluation Study (111)</td>
<td>24 to 50 mo</td>
<td>In patients, mean age 68 yr, with LVEF ≤35%, compared with placebo, trandolapril reduced mortality 33% in patients with anterior MI and 14% in patients without anterior MI.</td>
</tr>
<tr>
<td>Heart Outcomes Prevention Evaluation Study (20)</td>
<td>4.5 yr (up to 6 yr)</td>
<td>In patients aged ≥55 yr with MI (53%), cardiovascular disease (88%), or diabetes (38%) but no CHF or abnormal LVEF, ramipril reduced MI, stroke, and cardiovascular death 22%</td>
</tr>
<tr>
<td>EUROPA study (112)</td>
<td>4.2 yr</td>
<td>In patients, mean age 60 yr, with prior MI, compared with placebo, perindopril significantly reduced cardiovascular death, MI, or cardiac arrest by 20%</td>
</tr>
</tbody>
</table>

Abbreviations: MI, myocardial infarction; LVEF, left ventricular ejection fraction; CHF, congestive heart failure.
decrease in death from cardiovascular causes, a 37% reduction in development of severe CHF, a 22% decrease in development of CHF requiring hospitalization, and a 25% reduction in recurrent MI (108). Captopril decreased mortality independent of age, sex, blood pressure, LVEF, and use of thrombolytic therapy, aspirin, or β blockers (108). In the Heart Outcomes Prevention Evaluation Study, 9217 patients aged 55 years and older (55% aged ≥65 years) with MI (53%), cardiovascular disease (88%), or diabetes mellitus (38%) but no CHF or abnormal LVEF were randomized to ramipril 10 mg daily or placebo (20). At 4.5-year follow-up, compared with placebo, ramipril significantly reduced the incidence of MI, stroke, and cardiovascular death by 22% (95% CI, 0.70–0.86) (20). At 4.2-year follow-up of 13, 655 patients with prior MI and stable CAD in the EUROPA trial, compared with placebo, patients randomized to perindopril had a 20% significant reduction in cardiovascular death, recurrent MI, or cardiac arrest (112).

On the basis of the available data, ACE inhibitors should be administered to all patients after MI unless there are specific contraindications to their use (19,78).

**ALDOSTERONE ANTAGONISTS**

At 16-month follow-up of 6632 patients after MI with an LVEF less than or equal to 40% and either CHF or diabetes mellitus treated with ACE inhibitors or ARBs and 75% with β blockers, compared with placebo, patients randomized to eplerenone 50 mg daily had a significant 15% reduction in mortality and a 13% significant reduction in death from cardiovascular causes or hospitalization for cardiovascular events. (113). The ACC/AHA guidelines recommend an aldosterone antagonist in patients after MI treated with ACE inhibitors plus β blockers if they have an LVEF less than or equal to 40% with either CHF or diabetes mellitus if they do not have significant renal dysfunction or hyperkalemia (19).

**CALCIUM CHANNEL BLOCKERS**

Teo et al. (84) analyzed randomized controlled trials comprising 20,342 patients that investigated the use of calcium channel blockers after MI. Mortality was insignificantly higher (relative risk = 1.04) in patients treated with calcium channel blockers (84). A meta-analysis of randomized, clinical trials of the use of calcium channel blockers in patients with MI and both unstable and stable angina pectoris showed that the relative risk for mortality in the trials using dihydropyridines such as nifedipine that increase heart rate was 1.16 (114). The calcium channel blockers diltiazem and verapamil, which reduce heart rate, had no effect on survival (114).

Furberg et al. (115) performed a meta-analysis of the effect of nifedipine on mortality in 16 randomized secondary prevention clinical trials in patients with CAD. In this study, the relative risk for mortality was 1.06 for patients treated with nifedipine 30 to 50 mg daily, 1.18 for patients treated with nifedipine 60 mg daily, and 2.83 for patients treated with nifedipine 80 mg daily (115).

The Multicenter Diltiazem Postinfarction Trial demonstrated at 25-month follow-up in patients after MI that compared with placebo, diltiazem caused no significant effect on mortality or recurrent MI (116). However, in patients with pulmonary congestion at baseline or an LVEF less than 40%, diltiazem caused a significant increase in new cardiac events (hazard ratios = 1.41 and 1.31, respectively) (116). In this study, diltiazem also increased the incidence of late-onset CHF in patients with an LVEF less than 40% (117).
Use of a calcium channel blocker instead of a β blocker after MI in a New Jersey Medicare population also doubled the risk of mortality (98).

Since no calcium channel blocker has been shown to improve survival after MI except for the subgroup of patients with normal LVEF treated with verapamil in the Danish Verapamil Infarction Trial II (118), calcium channel blockers should not be used in the treatment of patients after MI. However, if patients after MI have persistent angina pectoris despite treatment with β blockers and nitrates, a nondihydropyridine calcium channel blocker such as verapamil or diltiazem should be added to the therapeutic regimen if the LVEF is normal. If the LVEF is abnormal, amlodipine or felodipine should be added to the therapeutic regimen. The ACC/AHA guidelines state that there are no class I indications for the use of calcium channel blockers after MI (19,78).

**ANTIARRHYTHMIC THERAPY**

**Class I Drugs**

A meta-analysis of 59 randomized controlled trials comprising 23,229 patients that investigated the use of quinidine, procainamide, disopyramide, imipramine, moricizine, lidocaine, tocainide, phenytoin, mexiletine, aprindine, encaainide, and flecainide after MI demonstrated that mortality was significantly higher in patients receiving class I antiarrhythmic drugs than in patients receiving no antiarrhythmic drugs (odds ratio = 1.14) (84). None of the 59 studies showed a decrease in mortality by class I antiarrhythmic drugs (84).

In the Cardiac Arrhythmia Suppression Trials I and II, older age also increased the likelihood of adverse effects including death in patients after MI receiving encaainide, flecainide, or moricizine (119). Compared with no antiarrhythmic drug, quinidine or procainamide did not decrease mortality in older patients with CAD, normal or abnormal LVEF, and presence versus absence of ventricular tachycardia (120). On the basis of the available data, patients after MI should not receive class I antiarrhythmic drugs.

**d,l-Sotalol and d-Sotalol**

Studies comparing the effect of d,l-sotalol with placebo on mortality in patients with complex ventricular arrhythmias have not been performed. Compared with placebo, d,l-sotalol did not reduce mortality in post-MI patients followed for one year (121). In the Survival with Oral d-Sotalol (SWORD) trial, 3121 survivors of MI with an LVEF less than or equal to 40% were randomized to d-sotalol or placebo (122). Mortality was significantly higher at 148-day follow-up in patients treated with d-sotalol (5.0%) than in patients treated with placebo (3.1%) (122). On the basis of the available data, d,l-sotalol, and d-sotalol should not be used to treat patients after MI.

**Amiodarone**

In the European Myocardial Infarction Amiodarone Trial, 1486 survivors of MI with an LVEF less than or equal to 40% were randomized to amiodarone (743 patients) or to placebo (743 patients) (123). At two-year follow-up, 103 patients treated with amiodarone and 102 patients treated with placebo had died (123). In the Canadian Amiodarone Myocardial Infarction Arrhythmia Trial, 1202 survivors of MI with nonsustained ventricular tachycardia or complex ventricular arrhythmias were randomized to amiodarone or to placebo (124). Amiodarone was very effective in suppressing ventricular tachycardia.
and complex ventricular arrhythmias. However, the mortality rate at 1.8-year follow-up was not significantly different in the patients treated with amiodarone or placebo (124). In addition, early permanent discontinuation of drug for reasons other than outcome events occurred in 36% of patients taking amiodarone (124).

In the Sudden Cardiac Death in Heart Failure Trial, 2521 patients, mean age 60 years, with class II or III CHF, an LVEF of less than or equal to 35%, and a mean QRS duration on the resting ECG of 120 milliseconds, were randomized to placebo, amiodarone, or an automatic implantable cardioverter-defibrillator (AICD) (125). At 46-month median follow-up, compared with placebo, amiodarone insignificantly increased mortality by 6% (125). At 46-month median follow-up, compared with placebo, ICD therapy significantly reduced all-cause mortality by 23% (125).

In the Cardiac Arrest in Seattle: Conventional Versus Amiodarone Drug Evaluation Study, the incidence of pulmonary toxicity was 10% at two years in patients receiving amiodarone in a mean dose of 158 mg daily (126). The incidence of adverse effects for amiodarone also approaches 90% after five years of therapy (127). On the basis of the available data, amiodarone should not be used in the treatment of patients after MI.

β Blockers

However, β blockers have been demonstrated to reduce mortality in patients with nonsustained ventricular tachycardia or complex ventricular arrhythmias after MI in patients with normal or abnormal LVEF (29,30,128,129). On the basis of the available data, β blockers should be used in the treatment of older patients after MI, especially if nonsustained ventricular tachycardia or complex ventricular arrhythmias are present, unless there are specific contraindications to their use.

Automatic Implantable Cardioverter-Defibrillator

In the Antiarrhythmics Versus Implantable Defibrillators (AVID) trial, 1016 patients, mean age 65 years, with a history of ventricular fibrillation or serious sustained ventricular tachycardia were randomized to an AICD or to drug therapy with amiodarone or d,l-sotalol (130). Patients treated with an AICD had a 39% reduction in mortality at one year, a 27% decrease in mortality at two years, and a 31% reduction in mortality at three years (130). If patients after MI have life-threatening ventricular tachycardia or ventricular fibrillation, an AICD should be inserted. The efficacy of the AICD implanted for ventricular fibrillation or recurrent sustained ventricular tachycardia on survival is similar in older and younger patients (131).

The Multicenter Automatic Defibrillator Implantation Trial (MADIT) randomized 196 patients with prior MI, an LVEF less than or equal to 35%, a documented episode of asymptomatic nonsustained ventricular tachycardia, and inducible ventricular tachycardia or ventricular fibrillation not suppressed by intravenous procainamide, or an equivalent drug at electrophysiologic study to conventional medical therapy or implantation of an AICD (132). At 27-month follow-up, patients treated with an AICD had a 54% reduction in mortality (132). These data favor the prophylactic implantation of an AICD in post-MI patients at very high risk for sudden cardiac death.

MADIT II randomized 1232 patients, mean age 64 years, with a prior MI and an LVEF of less than or equal to 30% to an AICD or to conventional medical therapy (133). At 20-month follow-up, compared with conventional medical therapy, the AICD significantly reduced all-cause mortality from 19.8% to 14.2% (hazard ratio = 0.69; 95% CI, 0.51–0.93) (133). The effect of AICD therapy in improving survival was similar in
patients stratified according to age, sex, LVEF, New York Heart Association class, and QRS interval (133).

In MADIT II, the reduction in sudden cardiac death in patients treated with an AICD was significantly reduced by 68% in 574 patients aged below 65 years (p = 0.02), by 65% in 455 patients aged 65 to 74 years (p = 0.005), and by 68% in 204 patients aged 75 years or older (p = 0.05) (134). The median survival in 348 octogenarians treated with AICD therapy was more than four years (135). These data favor considering the prophylactic implantation of an AICD in postinfarction patients with an LVEF of less than or equal to 30%.

HORMONE REPLACEMENT THERAPY

The Heart Estrogen/Progestin Replacement Study (HERS) investigated in 2763 women with documented CAD the effect of hormonal replacement therapy versus double-blind placebo on coronary events (136). At 4.1-year follow-up, there were no significant differences between hormonal replacement therapy and placebo in the primary outcome (nonfatal MI or CAD death) or in any of the secondary cardiovascular outcomes. However, there was a 52% significantly higher incidence of nonfatal MI or death from CAD in the first year in patients treated with hormonal replacement therapy (relative hazard = 1.52; 95% CI, 1.01–2.29) than in patients treated with placebo (136). Women on hormonal replacement therapy had a significantly higher incidence of venous thromboembolic events (relative hazard = 2.89, 95% CI, 1.50–5.58) and a significantly higher incidence of gallbladder disease requiring surgery (relative hazard = 1.38, 95% CI, 1.00–1.92) than women on placebo.

The Estrogen Replacement and Atherosclerosis trial randomized 309 postmenopausal women, mean age 66 years, with coronary angiographic evidence of significant CAD to estrogen plus progestin, estrogen alone, or double-blind placebo (137). At 3.2-year follow-up, quantitative coronary angiography showed no between-group differences in progression of coronary atherosclerosis (137).

At 6.8-year follow-up in the HERS trial, hormonal replacement therapy did not reduce the risk of cardiovascular events in women with CAD (138). The investigators concluded that hormonal replacement therapy should not be used to reduce the risk of coronary events in women with CAD (138). At 6.8-year follow-up in the HERS trial, all-cause mortality was insignificantly increased 10% by hormonal replacement therapy (relative hazard = 1.10; 95% CI, 0.92–1.31) (138). The overall incidence of venous thromboembolism at 6.8-year follow-up was significantly increased by 208% with hormonal replacement therapy (relative hazard = 2.08; 95% CI, 1.28–3.40) (139). At 6.8-year follow-up, the overall incidence of biliary tract surgery was significantly increased by 48% (relative hazard = 1.48; 95% CI, 1.12–1.95), the overall incidence for any cancer was insignificantly increased by 19% (relative hazard = 1.19; 95% CI, 0.95–1.50), and the overall incidence for any fracture was insignificantly increased by 4% (relative hazard = 1.04; 95% CI, 0.92–1.31) (139).

The estrogen plus progestin component of the Women’s Health Initiative (WHI) study included 16,608 healthy postmenopausal women aged 50 to 79 years with an intact uterus who were randomized to estrogen plus progestin or to placebo (140). At 5.2-year follow-up, this component of the WHI study was prematurely discontinued because the excess risk of events included in the global index was 19 per 10,000 person-years (140). Absolute excess risks per 10,000 person-years included seven more coronary events, eight more strokes, eight more episodes of pulmonary embolism, and eight more invasive breast
cancers, while absolute risk reductions per 10,000 person-years included six fewer colorectal cancers and five fewer hip fractures (140).

On the basis of the available data, hormonal replacement therapy should not be used in postmenopausal women with CAD (19,78).

INFLUENZA VACCINATION

Evidence from cohort studies and a randomized clinical trial indicate that annual vaccination against seasonal influenza prevents cardiovascular morbidity and mortality in patients with cardiovascular disease (141). The ACC/AHA guidelines recommend influenza immunization with inactivated vaccine administered intramuscularly as part of secondary prevention in persons with CAD or other atherosclerotic vascular disease with a class I indication (141).

CORONARY REVASCULARIZATION

Medical therapy alone is the preferred treatment in older patients after MI. The two indications for coronary revascularization in older patients after MI are prolongation of life and relief of unacceptable symptoms despite optimal medical management. In a prospective study of 305 patients aged 75 years and older with chest pain refractory to at least two antianginal drugs, 150 patients were randomized to optimal medical therapy and 155 patients to invasive therapy (142,143). In the invasive group, 74% had coronary revascularization (54% coronary angioplasty and 20% coronary artery bypass graft surgery). During the six-month follow-up, one-third of the medically treated group needed coronary revascularization for uncontrollable symptoms. At six-month follow-up, death, nonfatal MI, or hospital admission for an acute coronary syndrome was significantly higher in the medically treated group (49%) than in the invasive group (19%) (142,143). Revascularization by percutaneous transluminal coronary angioplasty (see chap. 14) or by coronary artery bypass graft surgery (see chap. 13) is extensively discussed elsewhere. If coronary revascularization is performed, aggressive medical therapy must be continued.

REFERENCES

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Management of the Older Patient After Myocardial Infarction


Management of the Older Patient After Myocardial Infarction

13

Surgical Management of Coronary Artery Disease in the Elderly

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Since 1990, the U.S. population over the age of 65 years has been growing rapidly in both absolute and relative numbers. Currently, 36.8 million individuals are over 65 years of age. By 2010, when the first of the baby boomers (those born between 1946 and 1964) reach 65, there will be 40 million people aged 65 years or older. By 2030, when the last of the baby boomers reach 65, the number of individuals aged 65 years or older is projected to reach 70 million. Moreover, the elderly are living longer. In 1900, at age 65, 13% of men and 16% of women could expect to live to age 85 years. By 1992, these percentages were 30% and 50%, respectively. As the baby boomers age, the percentage of the population aged 85 years or older will grow from the current level of 1.4% to 2.4% in 2030 and to 4.6% in the year 2050. Octogenarians are, in fact, the fastest growing segment of the population in the United States (Table 1) (1,2).

While arthritis is the most common chronic disease borne by the elderly, heart disease is the most common cause of major disability in the elderly as well as the most common reason for hospitalization and death. Clinically evident heart disease affects 30% of those aged 65 years or older (1,3). Approximately 12% of the elderly population suffers from major limitations of activity because of heart disease (4). Forty percent of deaths in the over-65 population are due to heart disease (5). Clinically recognized ischemic heart diseases (and its complications) are responsible for 70% of the deaths due to heart disease (6,7).

In 1993, 7–8% of men and women aged 65 years or older were hospitalized for “diseases of the heart,” with an average hospital stay of six to seven days (1,8). Congestive heart failure (CHF) was the most common reason for hospitalization (9), but from 6% to 9% of the elderly discharged with a diagnosis of “diseases of the heart” had
undergone coronary arterial bypass grafting (CABG) at an estimated cost of $6 billion to $7 billion per year (8,10–15).

As modern medical treatment is being employed for increasing numbers of progressively older patients, dire predictions about the solvency of Social Security and Medicare abound. By 2030, the number of individuals over the age of 65 will be more than double (2). It has been suggested that by 2050 outflow of funds from Social Security and Medicare will exceed inflow by 75% (16). Rationing (in one form or another) of health care coverage for the elderly is being discussed openly. Health care planners question whether the rapidly increasing expenditure of funds, particularly for highly technical procedures, is justified in a population that is nearing the end of life or, at least, the end of active life (17).

It is against this background that the merits of performing CABG in the elderly must be discussed. Before deciding whether or not the benefits that the elderly reap from sophisticated surgical procedures are worth the risks and the costs, however, it is important to appreciate the characteristics of the population commonly referred to as elderly. How sick, impaired, and disabled are the elderly? How prevalent is coronary artery disease (CAD) in the elderly? Does the nature and presentation of CAD in the elderly differ from that in a younger population? Can current medical and surgical treatments of ischemic heart disease prevent disabilities, restore function, prolong life, and increase the quality of life in the elderly with CAD?

### CHARACTERISTICS OF THE OVER-65 POPULATION

Most discussions about the elderly center on prevalence of disease, degrees of physical or mental impairment, need for hospitalization or institutionalization, and end-of-life expenses. Indeed, 80% of the elderly population does suffer from one or more chronic conditions. Overall, however, the elderly population is surprisingly healthy. Only 20% of those in the 65- to 74-year-old group have major or severe limitations of activities because of their chronic diseases (Table 2) (18). Only 5% reside in institutions (many temporarily) (19). In 1994, 77% of those older than 65 years of age were living in their own houses. Of these, 55% were living with their spouses; 30% lived alone but independently; 12% lived with other relatives; only 2% resided with nonrelatives (20). Half of those aged 85 or older still live alone or with their spouses (21). In the community, about 5% of the elderly

<table>
<thead>
<tr>
<th>Years</th>
<th>Resident population (in 1000s)</th>
<th>≥65</th>
<th>≥85</th>
<th>≥65</th>
<th>≥85</th>
<th>At birth</th>
<th>At age 65</th>
</tr>
</thead>
<tbody>
<tr>
<td>1900</td>
<td>75995</td>
<td>3116</td>
<td>125</td>
<td>4.1</td>
<td>0.2</td>
<td>49.2</td>
<td>11.9</td>
</tr>
<tr>
<td>1995</td>
<td>263434</td>
<td>33648</td>
<td>3598</td>
<td>12.8</td>
<td>1.4</td>
<td>76.3</td>
<td>17.7</td>
</tr>
<tr>
<td>2010</td>
<td>297716</td>
<td>40104</td>
<td>5671</td>
<td>13.2</td>
<td>1.9</td>
<td>77.9</td>
<td>18.6</td>
</tr>
<tr>
<td>2030</td>
<td>346899</td>
<td>70175</td>
<td>8455</td>
<td>20.0</td>
<td>2.4</td>
<td>78.8</td>
<td>20.0</td>
</tr>
<tr>
<td>2040</td>
<td>369980</td>
<td>80109</td>
<td>13552</td>
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</tr>
<tr>
<td>2050</td>
<td>393931</td>
<td>77014</td>
<td>18223</td>
<td>20.0</td>
<td>4.6</td>
<td>79.8</td>
<td>21.6</td>
</tr>
</tbody>
</table>
have some clinically detectable impairment of cognitive function but only 2% of the elderly have major limitations of activity because of mental or nervous disease (22). Seventy percent of the elderly rate their health as good, very good, or excellent (23). Whatever the nature, degree, and permanence of their disabilities might be, it is apparent that the chronic diseases that cause severe disability and death in the elderly can be treated very successfully by currently available methods (Tables 3 and 4). It is also apparent that heart disease stands out as the most common chronic disease that results in major limitations of activity and death in the elderly (4,18,24).

<table>
<thead>
<tr>
<th>Table 2</th>
<th>Percentage of Noninstitutionalized Population Whose Activities Are Limited by One or More Chronic Conditions</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age group (yr)</td>
<td>None</td>
</tr>
<tr>
<td>65 or older</td>
<td>61.2</td>
</tr>
<tr>
<td>65 to 74</td>
<td>65.6</td>
</tr>
<tr>
<td>75 or older</td>
<td>54.7</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Table 3</th>
<th>Percentage of Population Age 65 or Older with Major Limitations of Activities Because of Specific Conditions</th>
</tr>
</thead>
<tbody>
<tr>
<td>Disease/condition</td>
<td>Major limitations (%)</td>
</tr>
<tr>
<td></td>
<td>Men</td>
</tr>
<tr>
<td>Heart</td>
<td>12</td>
</tr>
<tr>
<td>Arthritis</td>
<td>8</td>
</tr>
<tr>
<td>Visual impairment</td>
<td>4</td>
</tr>
<tr>
<td>Emphysema</td>
<td>4</td>
</tr>
<tr>
<td>Hypertension</td>
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</tr>
<tr>
<td>Cerebrovascular disease</td>
<td>3</td>
</tr>
<tr>
<td>Mental/nervous</td>
<td>2</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>3</td>
</tr>
<tr>
<td>Other circulatory</td>
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<table>
<thead>
<tr>
<th>Table 4</th>
<th>Selected Causes of Death in Patients Aged 65 and Above (1992)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cause</td>
<td>Number</td>
</tr>
<tr>
<td>All causes</td>
<td>735,298</td>
</tr>
<tr>
<td>Heart disease</td>
<td>271,214</td>
</tr>
<tr>
<td>Cancer</td>
<td>191,204</td>
</tr>
<tr>
<td>Stroke</td>
<td>46,722</td>
</tr>
<tr>
<td>Obstructive pulmonary disease</td>
<td>42,961</td>
</tr>
<tr>
<td>Pneumonia/influenza</td>
<td>30,374</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>14,865</td>
</tr>
<tr>
<td>Accidents</td>
<td>13,335</td>
</tr>
</tbody>
</table>
PREVALENCE OF CAD IN THE ELDERLY

While there is general agreement that prevalence of CAD increases markedly with increasing age, the true prevalence of CAD in the elderly is difficult to determine. About 28% of those over 65 die from ischemic heart disease (6,7). Epidemiological studies, relying on history and resting electrocardiographs, have found symptomatic coronary disease in 20–22% of the general population over 70 (25,26). When rest and stress criteria are combined, at least half of those over 70 were found to have CAD (27). Autopsy studies indicate the prevalence of significant CAD (stenosis ≥60% of at least one coronary artery) to be as high as 60–70% in the elderly (28).

EVOLUTION OF THE TREATMENT OF CAD

Evolution of the treatment of CAD took place over a period of 200 years. During the 18th century, angina pectoris was recognized as a common and lethal illness that frequently attacked without warning and was associated with sudden death. Its relationship to arterial disease was recognized. During the 19th century, the basic instruments necessary for detecting CAD were developed, as were the basic medications for treating its symptoms. Myocardial infarction (MI) was recognized as a pathological entity. The early and mid 20th century saw the development of sophisticated diagnostic techniques that made modern treatment of CAD and its complications a reality during the last half of the 20th century.

Recognition of Angina Pectoris

Twenty-four hundred years ago, Hippocrates noted that frequent attacks of pain in the heart in an old person often predicted sudden death. Treatises describing the pulse and its abnormalities date far back in history, as do descriptions of the anatomy of the heart. Nevertheless, appreciation and understanding of the role of the coronary arteries in the production of cardiac disease did not begin to develop until the late 18th century when Heberden introduced the term angina pectoris (Greek for strangling or choking and breastbone or breast) during a lecture before the Royal College of Physicians of London in July, 1768. He described symptoms he had observed in “at least twenty men almost all above 50 years old, most with a short neck, and inclining to be fat.” Heberden commented that angina pectoris was “not extremely rare,” that it was associated with walking, particularly after eating, and that the uneasiness vanished the moment the patient stood still. He noted the symptoms worsened with time and could occur while lying down. He reported that although the natural tendency of the illness was to kill the patient suddenly, the disorder could last “near 20 years.” Because the patient’s pulse was not usually disturbed by the pain, Heberden concluded that “the heart is not disturbed by it.” He ascribed the illness to “a strong spasm sometimes accompanied by an ulcer,” but commented that he had never had it in his power to “see anyone opened who had died of it.” Heberden published his report in 1772 (29–31).

In 1775, Edward Jenner helped his close friend, John Hunter, perform an autopsy on one of Heberden’s patients who had died suddenly following an anginal attack associated with a sense of impending death. Ossified coronary vessels were found but the arteries were not examined carefully. In 1785, Jenner made the connection between angina pectoris and CAD but did not publish his conclusions until 1799 (in a letter to Parry who included it in his text, Syncope Anginosa). John Hunter, who had developed angina
pectoris in 1773, finally died of the disease in 1793, at age 65. His death occurred suddenly during a dispute with the board of St. George’s Hospital. Jenner’s delay in reporting his conclusions about the basis of angina pectoris until after Hunter’s death has been attributed to his desire not to alarm his life-long friend (32–34).

Defining the Pathophysiology of CAD

Although the frightening and disabling nature of angina pectoris was clearly recognized as a major clinical problem during the 19th century; little that was new was added to the basic understanding of CAD during that time. In his 1809 textbook on diseases of the heart, Burns attributed angina pectoris to myocardial ischemia. In 1819, Laennec introduced the stethoscope. In 1840, Williams suggested that obstruction of a coronary artery was the cause of the pallid, yellowish appearance of a segment of myocardium discovered at autopsy. The term myocardial infarction was not then in use (as late as 1884, what is now known as a myocardial infarction was referred to as “fibrinoid degeneration”). In 1867, Brunton introduced amyl nitrite for the treatment of angina pectoris. Nitroglycerin, the mainstay of the treatment of angina pectoris even today, was introduced by Murrell in 1879. Riva-Rocci developed the first practical sphygmomanometer in 1891. The year following the serendipitous discovery of X rays by Wilhelm Conrad Roentgen, in 1895, roentgen studies of the heart were being performed by Williams. That same year, Pierre Marie writing his thesis on complications of cardiac disease used the term MI. Dock, in 1896, was the first physician in the United States to make a diagnosis of coronary thrombosis during life (32,35,36). Widespread appreciation of the relationship between CAD, angina pectoris, and MI did not occur until the second quarter of the 20th century. Sir Clifford Allbutt, in 1900, attributed angina pectoris to disease of the aorta, an understandable conclusion in view of the likelihood of coronary ostial occlusion secondary to the syphilitic aortitis that was so common at the time (36). A major contribution to establishing the pathophysiology of coronary arterial disease was made by Einthoven in 1903, when he developed a practical method for performing electrocardiography. Sir William Osler commented in 1910 that he did not see a case of coronary thrombosis until he became a Fellow of the Royal College of Physicians (37). CAD remained virtually unrecognized as a cause of death until 1912, when Herrick described (in six patients) the clinical features of sudden obstruction of the coronary arteries, including the gross changes that occurred in the myocardium in the region of the infarct. He noted that, while previous attacks of angina had generally been experienced by the patient, fatal coronary arterial thrombosis might be the first evidence of coronary disease (38). In 1918, he republished his data and reported electrocardiographic studies conducted in patients with coronary artery thrombosis (39). While commented that, in the mid 1920s, at Massachusetts General Hospital diagnoses of coronary artery thrombosis and MI were rare among the autopsies performed (31). He stated that he did not see his first patient with a MI until he was in his second year of practice in 1921. In 1923, Wearn wrote that “coronary thrombosis with infarction of the heart as a clinical entity is a condition which is generally classed among the rarities of medicine” (37). The most famous instance of failure to recognize the signs and symptoms of fatal coronary arterial disease occurred in San Francisco on August 2, 1923, when Warren Harding, the 29th president of the United States, died following an acute MI. His death was attributed to acute indigestion or (by the New York Times) to a “stroke of apoplexy.” By the late 1920s, however, coronary thrombosis—alias MI—was a well-established diagnosis.
Development of Modern Diagnostic Techniques

In 1929, a German intern, Werner Forssmann, having heard of an experiment by Claude Bernard, threaded a catheter through his antecubital vein into his right atrium. His goal was to devise a technique to speed delivery of drugs to a patient and, in addition, to understand the mysteries of the heart and circulatory system (40,41). Discouraged from pursuing his experiments by Sauerbruch, the professor of surgery, Forssmann became a urologist. Courand became aware of Forssmann’s work and by 1941 had developed a technique for catheterizing the right heart in humans (42). Zimmerman in 1950 and Seldinger in 1953 developed the techniques of left heart catheterization. In 1958, F. Mason Sones, Jr., accidentally injected the right coronary artery with contrast material producing the first selective coronary angiogram performed in a human being. Louis Pasteur is credited with the statement “chance favors the prepared mind.” Sones not only recognized the potential value of his serendipitous observation but pursued development of the technique of selective coronary arteriography to make it a practical diagnostic technique. The presentation of his results during the 1959 meeting of the American Heart Association introduced the modern era of medical and surgical treatment of CAD (43).

Natural History of Patients with Angina Pectoris

Only 30–40% of 70-year-old individuals with anatomically significant disease of one or more coronary arteries will be overtly symptomatic (with classical angina pectoris or evidence of a MI on a resting electrocardiogram) (25,27). Of those who have symptomatic CAD, about 37% of men and 65% of women will have angina pectoris as the initial manifestation of the disease. If death as an initial manifestation of symptomatic CAD is excluded, then about 40% of men and 70% of women with CAD will be present with angina pectoris as their initial symptom (44,45) (Table 5). Since severe and/or intractable angina pectoris is the major indication for 75–95% of the CABGs performed in the United States, particularly in the elderly, an understanding of the natural history of those with angina pectoris must be the foundation for evaluating the effectiveness of medical or surgical therapy of CAD.

Unfortunately, the natural history of angina pectoris is difficult to document. Early studies by Herrick (1918) and by White (1926, 1931, 1943) were handicapped because investigators lacked the technology to determine the extent of disease in the coronary arteries during life (39,46–48). In addition, patients with angina pectoris complicated by associated diseases such as hypertension, valvular heart disease, MI, and CHF were often included with those who suffered from uncomplicated angina pectoris.

Table 5 Distribution and Frequency of Initial Manifestations of Coronary Heart Disease in 492 Individuals from the Framingham Study

<table>
<thead>
<tr>
<th>Manifestation</th>
<th>Men</th>
<th>Women</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Number</td>
<td>Percent</td>
<td>Number</td>
</tr>
<tr>
<td>Angina pectoris</td>
<td>119</td>
<td>37</td>
<td>110</td>
</tr>
<tr>
<td>Coronary insufficiency</td>
<td>23</td>
<td>7</td>
<td>12</td>
</tr>
<tr>
<td>Myocardial infarction</td>
<td>139</td>
<td>43</td>
<td>30</td>
</tr>
<tr>
<td>Death</td>
<td>42</td>
<td>13</td>
<td>17</td>
</tr>
<tr>
<td>Total</td>
<td>323</td>
<td>100</td>
<td>169</td>
</tr>
</tbody>
</table>
In these early series the annual mortality of patients with angina pectoris ranged from 2.5% to 9.0% (49).

In 1952, Block et al. (50) described 5- and 10-year survivals by age group for 6882 patients in whom a diagnosis of angina pectoris had been made. The study population included patients with cardiac enlargement, CHF, and MI. Table 6 summarizes their results. Annual mortality (averaged >10 years) for the entire group was 6.0%. Annual mortality was greatest during the first year (15.3%) then decreased in subsequent years. Overall, 5-year survival for the group was 58%; 10-year survival was 37%. Expected survivals in a general population of like ages would have been 87% at 5 years and 70% at 10 years.

In 1971, Gordon and Kannel (44) reported the frequency with which coronary events occurred during a 14-year follow-up of 5209 people randomly sampled from a general population. One hundred and ninety-seven persons developed angina pectoris as their initial manifestation of CAD. The risks of dying in this group of individuals varied with the severity of their symptoms. Annual mortality for those free of heart disease was 1/1000. For those in New York Heart Association (NYHA) class I, the risk of dying was 4/1000/yr; for those in NYHA class II, the risk was 19/1000/yr, and for those in classes III or IV, 43/1000/yr. In 1972, Kannel and Feinleib (45) reported presentations and outcomes in 492 persons who first developed CAD during the 14-year follow-up of a general population of 5127 individuals from the Framingham study (Table 5). Coronary angiography was not performed in these patients. Of the 492 people, 229 presented with angina pectoris. Two hundred of these manifested “uncomplicated” angina pectoris; that is, angina not complicated by MI, coronary insufficiency, or coronary death. Forty percent of the men with uncomplicated angina and 40% of women aged 60 years and older with uncomplicated angina died within eight years. Only 15% of women under age 60 with uncomplicated angina died during the eight years. Annual mortality was 4% for men with uncomplicated angina pectoris. Over a period of five years, MI was relatively uncommon in women with angina pectoris (7%) but occurred in 24% of men. Half of the men over age 45 years with angina suffered a MI within eight years.

While studies conducted in the 1950s and 1960s could relate the effects of age, severity of symptoms, and presence of associated cardiac diseases with outcome in patients with angina pectoris, it was not until coronary arteriography became widely available that it was possible to correlate the natural history of these patients with the extent of their coronary disease. In 1972, Oberman (51) analyzed the course of 246 patients with angina but without associated cardiovascular disease or serious non-cardiovascular disease. All had undergone coronary arteriography between 1965 and

### Table 6  Prognosis of Angina Pectoris: Survival Rates of Patients with Angina Pectoris

<table>
<thead>
<tr>
<th>Age group (yr)</th>
<th>Number of patients</th>
<th>Percentage alive at</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>5 Yr</td>
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<tr>
<td>&lt;40</td>
<td>112</td>
<td>66.1</td>
</tr>
<tr>
<td>40–49</td>
<td>935</td>
<td>65.2</td>
</tr>
<tr>
<td>50–59</td>
<td>2067</td>
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<tr>
<td>70–79</td>
<td>572</td>
<td>42.8</td>
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<tr>
<td>≥80</td>
<td>34</td>
<td>26.5</td>
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1970, a time period prior to the advent of aortocoronary bypass grafting in their institution. At 22 months, there were no deaths in patients with one-vessel disease and small hearts or in those with one-vessel disease and no electrocardiographic evidence of an old transmural infarction. The annual mortality for all patients with one-vessel disease was 2.0%. Annual mortality for patients with two-vessel disease was 13.0% and for three-vessel disease, 15.0%. The presence of an old MI, a history of CHF, or an enlarged heart markedly increased the annual mortality in patients with angina pectoris. In 1974, Reeves et al. (49) analyzed the course of 705 patients who had undergone coronary arteriography prior to 1970. The annual mortality for the entire group was 6.5%. For one-vessel disease, annual mortality was 2.2%; for two-vessel disease, 6.8%; and for three-vessel disease, 11.4%. In 1983, Proudfit et al. (52) presented 15-year survivals for 598 patients with chest pain treated medically following angiography. All but 64 were male. Annual mortality averaged over 10 years was 5.4% with a 31% 15-year survival.

Overall, the natural history of most patients with angina pectoris is poor with annual mortality rates for uncomplicated disease of 4–6%. However, angina pectoris alone is a poor predictor of survival (53). Individuals with single-vessel disease and angina pectoris uncomplicated by a history of transmural MI, CHF, cardiomegaly, associated cardiovascular disease, or serious noncardiovascular disease appear to have annual mortality rates of 1% or less (49). In the study by Oberman et al., the independent predictors of increased annual mortality in patients with angina pectoris followed for 22 months, in the order of their importance, were heart size, stenosis of the left anterior descending artery, dyspnea on effort with either paroxysmal nocturnal dyspnea or orthopnea, heart rate, stenosis of the left main coronary artery, stenosis of the left circumflex artery, and stenosis of the right coronary artery (51). The need to identify subsets of patients with CAD was to assume greater importance as the outcomes of CABG and percutaneous transluminal coronary angioplasty (PTCA) began to be evaluated.

**EVOLUTION OF SURGICAL TREATMENT**

At about the time of Herrick’s report that sudden occlusion of a major coronary artery was not “almost universally fatal,” surgeons began their attempts to relieve the pain of angina pectoris. François-Franck, in 1899, proposed removal of the cervical and first thoracic ganglia. His intent was to accomplish a complete cure of certain cases of Graves’ disease, which were complicated by aortitis and angina (54). Bilateral extirpation of the cervical sympathetic chain, together with removal of both thoracic ganglia for the treatment of angina pectoris, was first performed by a Bucharest surgeon, Jonnesco, in 1916 (55).

From 1916 through 1982, no less than 59 different varieties of surgical procedures were performed for the treatment of CAD. The procedures ranged from those designed to interrupt the afferent nerve pathways from the heart to those developed to replace the heart. These surgical approaches to CAD can be divided into four broad categories: extrapericardial procedures, techniques for indirect myocardial revascularization, direct revascularization of the coronary arteries, and cardiac replacement (41,56–58) (Table 7). A few of these procedures were performed only in experimental animals; some represented variations of a more basic concept; many were devised by more than one individual; most were performed in humans at one time or another often over a period of many years. Eventually, all but a few were found to be ineffective or minimally effective.

A major share of the credit for the development of modern coronary arterial surgery belongs to Claude Beck of Western Reserve University and to his persistent efforts to prevent sudden death in patients with a heart “too good to die.” Beginning in 1935, he...
devised and applied numerous variations of his Beck I and Beck II operations. He noted that increases of arterial flow of as little as 5 mL/min into anoxic areas of the myocardium could relieve the pain of angina pectoris and could afford protection against a fatal heart attack (59,60). About 10 years later, Arthur Vineberg of Montreal began advocating implantation of systemic arteries into the myocardium, thus beginning the era of indirect myocardial revascularization (61).

Two sentinel events in the 1950s made possible the modern era of myocardial revascularization. On May 6, 1953, the ability to operate on a quiet heart free of blood became a reality when John Gibbon successfully closed an atrial septal defect using a heart lung machine he and his wife had developed (62,63). In 1958, F. Mason Sones, Jr., provided the means to accurately identify, localize, and quantify coronary artery lesions (43,64).

Widespread application of the current techniques of direct myocardial revascularization began after the reports of Favoloro, Johnson, Urschel, and Kerth in 1969 (64–67). The first transplantation of a human heart was performed by Christiaan Barnard in South Africa in 1967 (68). On September 16, 1977, Andreas Gruentzig, in Zurich, performed the first balloon dilatation of a coronary artery in a human. The technique was referred to as PTCA and was quickly adopted as an alternative to CABG (41). In the mid-1970s, 70,000 CABGs were performed annually in the United States (64). By 1994, the number had grown to 318,000 per year (69).

As early as 1971, however, there were those who questioned the efficacy of aortocoronary bypass grafting and the justification for its widespread application. The objections and criticisms were based in part on the past history of failures and marginal results of surgical procedures intended to treat CAD, in part on what were considered to be the high risks inherent in coronary artery surgery, and in part on the availability of techniques of medical management that presumably could yield results comparable with or superior to those achieved by operation. These concerns led to the performance of numerous controlled studies that compared the outcomes of medical and surgical therapy.
The advent of PTCA led to additional randomized studies comparing PTCA with CABG and with medical treatment.

OUTCOME OF RANDOMIZED STUDIES

Since 1972, five large randomized studies have compared the results of coronary arterial bypass plus medical therapy with intensive medical therapy of angina pectoris. Stable angina pectoris was the subject of three studies; unstable angina was the subject of two studies. More recently, two more randomized studies have compared outcomes in patients treated by PTCA and CABG. While various criticisms can be made of the design and conduct of these studies, it is important to summarize their findings since the conclusions drawn from them have shaped the indications for CABG in patients of all ages.

Early Veterans Administration Studies

In the mid-1960s, cardiologists and thoracic surgeons in the Veterans Administration (VA) developed a keen interest in evaluating current surgical procedures to revascularize the ischemic heart. Three operations were studied, each in increasing detail, employing randomization techniques: The Beck “poudrage” procedure, the Vineberg implant procedure, and direct revascularization procedures. Analyses of the Beck procedure did not reach the literature. In the study of the Vineberg procedure, a total of 146 patients (75 medical and 71 surgical) were randomized between 1966 and 1972. Thirty-day operative mortality (OM) was 12.3%. Visualization of the implant one year after operation was accomplished in half of the eligible patients. Fifty percent of the patients with single implants and 69% of those with double implants were found to have patent grafts. At 12 years, 41% of the medical group and 42% of the surgical group were alive. Eighty-one percent of the deaths in both the medical and surgical groups were due to cardiac disease. The degree of revascularization achieved by the implants did not improve survival. The study ended partly because of these findings and partly because of the shift to direct revascularization of the coronary arteries (70).

VA Stable Angina Study

Six hundred and eighty-six patients were entered into the stable angina study between 1972 and 1974. Three hundred and fifty-four individuals were randomized to medical therapy; 332 were randomized to medical plus surgical therapy. Ninety-one patients had greater than 50% stenosis of the left main coronary artery (43 medical, 48 surgical). Five hundred and ninety-five patients were “non–left main” (311 medical and 284 surgical). All patients were men. There were no age restrictions. The age range of those in the study was 27 to 68 years with a mean age of 50.5 years. Forty-four percent of the patients were less than 50 years old. Patients with all degrees of angina were accepted. There was no minimum ejection fraction set for selection. During 11 years of follow-up, 38% of the 354 patients assigned to medical treatment underwent bypass surgery. Twenty-two of those crossing over had left main CAD.

At 11 years, survival for patients without significant left main disease was 58% in both treatment groups. Survival between treatment groups of patients with one-vessel or three-vessel disease was not significantly different at either 7 or 11 years. At 11 years, survival for patients with two-vessel disease treated surgically was marginally worse than for their counterparts treated medically (55% vs. 69%; \( p = 0.045 \)). Patients treated...
surgically for left main disease clearly did better than those treated medically (88% vs. 65%, \( p = 0.016 \)). Patients who were categorized as high risk by angiographic and/or clinical criteria had significantly better survival with surgical treatment. Patients were classified as angiographically high risk if they had three-vessel disease and impaired left ventricular function. They were classified as clinically high risk if they had at least two of the following: resting ST depression, a history of MI, or a history of hypertension. Survival at 11 years in the high clinical risk group was 49% for the surgical group and 36% for the medical group (\( p = 0.015 \)). In the low clinical risk group, survival at 11 years was 63% for the surgical group and 73% for the medical group (\( p = 0.066 \)). In the angiographic high-risk group, survival at 11 years was 50% for surgical patients and 38% for medical patients (\( p = 0.026 \)). In the angiographic low-risk group, the corresponding survival data were 61% and 68% (\( p = 0.105 \)). In the combined high angiographic and clinical risk group, survival at 11 years was 54% in the surgical group and 24% in the medical group (\( p = 0.005 \)). Corresponding survivals in the combined low angiographic and clinical risk group were 66% and 76% (\( p = 0.092 \)). The average annual mortality rates during the first seven years of the study were 3.3% for all surgically treated patients without left main disease and 4.0% for all medically treated patients without left main disease. During the next four years, the corresponding annual mortality rates were 4.8% and 3.5%. Thus, three groups of patients benefited from surgical treatment: those with significant left main disease; those with extensive coronary arterial disease associated with reduced ventricular function; and those who fell into clinical or angiographic high-risk categories.

Quality of life was better in those patients treated surgically. At 5 years, 41% of surgical patients and 17% of medical patients reported marked improvement in symptoms. Twenty percent of the surgical patients and 42% of the medical patients described worsening symptoms. Over the five-year period, the benefits of surgery decreased, but at 5 years were still significantly better than medically treated patients (\( p = 0.0014 \)). The incidence of nonfatal MI was not significantly different between the two treatment groups. At five-year follow-up, left ventricular function remained unchanged in both treatment groups (71–74).

**VA Unstable Angina Study**

Four hundred and sixty-eight patients were entered into the unstable angina study between 1976 and 1982 (237 medical, 231 medical plus surgical). Three hundred and seventy-four patients were identified as Type I (accelerated angina, rest angina, and recent-onset angina); 94 were identified as Type II (prolonged angina unrelieved by nitrates and accompanied by ST-segment changes on electrocardiogram). All patients were men. There were no age restrictions. The age range in the study was 32 to 73 years, with a mean age of 56 years. Patients with all degrees of angina were accepted. Patients with ejection fractions below 30% and those with left main lesions greater than 50%, recent MI, or prior coronary artery surgery were excluded. At the end of 10 years, 50% of patients randomized to medical treatment had crossed over to surgery.

At 10 years, survival was 61% for surgical patients and 62% for medical patients. At five years and eight years, there was significantly better survival for patients with three-vessel disease treated surgically (89% vs. 77% and 77% vs. 65%, respectively). At 10 years, however, the surgical advantage was no longer significant (63% vs. 57%; \( p = 0.190 \)). At eight years, survival of patients with three-vessel disease and an ejection fraction of 58% or less was significantly better in the surgical group (79.5% vs. 57.1%; \( p = 0.018 \)). In contrast, survival at eight years in those with one- or two-vessel disease and
an ejection fraction greater than 58% was significantly better with medical treatment (83.2% vs. 67.8%; \( p = 0.022 \)).

A major finding in this study was the effect of surgical treatment on survival of patients with an ejection fraction between 30% and 58% if the crossovers from medicine to surgery were censored (counted as lost to follow-up at the time of crossover). When this was done, there was a strong advantage to surgical treatment throughout the 10 years of follow-up (59% vs. 43%; \( p = 0.007 \)) (75).

Continued smoking was an independent predictor of death in the surgical group at 2, 5, and 10 years. At 10 years, NYHA class III or IV, age, and diabetes mellitus (DM) were additional independent predictors of mortality in the surgical group. In the medically treated group, decreased ejection fraction and the number of vessels diseased were consistent, independent predictors of mortality.

As in the stable angina study, quality of life was better in the surgical patients who had superior pain control, reduced medication requirements, and significantly fewer new cardiovascular hospitalizations over the 10-year observation period (\( p = 0.0001 \)). At the end of 10 years, the number of nonfatal MIs was not significantly different between the treatment groups (76–79).

EUROPEAN CORONARY SURGERY STUDY GROUP

Seven hundred and sixty-eight patients were entered into the study between 1973 and 1976 (373 medical, 395 surgical). One patient was lost to follow-up before operation, leaving 394 surgical patients. All were men under the age of 65 years (mean age 50 years). Those with severe angina pectoris as well as those with ejection fractions below 50% or single-vessel disease were excluded from the study. Patients with left main lesions of 50% or more were included on a discretionary basis (31 medical, 28 surgical patients). Those assigned to medical treatment could cross over to the surgical group if they had unacceptable symptoms despite adequate medical therapy (24% did cross over within five years). All patients were followed for five years; 60% were followed for six years; 25% for seven years; and 10% for eight years.

At five years, 92.4% of the surgical patients and 83.6% of the medical patients were alive (\( p = 0.00025 \)). In those patients with left main disease, there was a markedly increased five-year survival with operation, but because of the small numbers, the difference was not significant (81.7% vs. 67.9%; \( p = 0.11 \)). Survival was markedly improved in the surgical group with three-vessel disease and also in the group with two- or three-vessel disease when it was associated with stenosis of 50% or greater in the proximal left anterior descending artery. An abnormal electrocardiogram, ST-segment depression of 1.5 mm or more during exercise, and the presence of peripheral vascular disease were each independent predictors of better survival with operation. Survival at 10 years in patients over the age of 53 years was significantly better in the surgical group (72% vs. 57%; \( p = 0.007 \)). Below age 53 years, age was not a significant factor affecting outcome between the two treatment groups. A conclusion drawn from the study was that the greatest benefits of surgery occurred in the high-risk groups of patients. Surgery was unlikely to improve five-year survivals in patients with good left ventricular function, ST-segment depression less than 1.5 mm on exercise, a normal resting electrocardiogram, and absence of peripheral vascular disease. These conclusions closely resemble those reached in both the stable and unstable VA randomized studies (79–82).

Operation markedly improved the quality of life as measured by the percentage of patients free of angina or by the degree of increased exercise tolerance. As in other
studies, these effects diminished with time, although the advantage over medical treatment remained statistically significant at four years for exercise performance ($p = 0.001$) and throughout the study for relief of angina ($p = 0.001$) (80).

**Coronary Artery Surgery Study**

In 1973 the National Heart, Lung, and Blood Institute organized a randomized trial designed to compare results of medical and surgical therapy in patients with CAD. The goal of the randomized trial was to test the hypothesis that coronary artery bypass surgery significantly reduced the mortality rate and the incidence of MI in patients with mild angina or in those who were asymptomatic after a MI (but who had CAD documented by angiography) (82,83).

Between 1975 and 1979, 780 patients were entered into the study (390 medical, 390 surgical). Ninety percent of the patients were men. All enrollees were 65 years of age or less; the mean age was 51.2 years. Patients with angina more severe than Canadian class II were excluded, as were those with unstable angina, progressive angina, CHF, previous coronary bypass surgery, or serious coexisting illness. Patients with an ejection fraction less than 35% and those with left main lesions greater than 70% were also excluded. Patients with a well-documented MI more than three weeks before randomization were accepted into the study. Analyses were performed on the basis of treatment assigned (79,83).

At eight years, 87% of the surgical patients and 84% of the medical patients were alive ($p = 0.14$). However, in the subset of patients with ejection fractions below 50%, 84% of the surgical patients and 70% of the medical patients were alive at seven years ($p = 0.012$). When this subset of patients was analyzed by the number of vessels diseased, a significant difference in survival was found only in those patients with three-vessel disease (88% in the surgical group, 65% in the medical group; $p = 0.0094$). There was no significant difference between the medical and surgical treatment groups in the occurrence of nonfatal MI. At five years, the crossover rate from medicine to surgery was 24% (82).

From the standpoint of quality of life at five years, the surgical group had significantly less chest pain ($p < 0.0001$), fewer limitations of activity ($p < 0.0001$), and a lower requirement for β-blockade ($p < 0.0001$). In the surgical group, treadmill exercise tests documented less exercise-induced angina, less ST-segment depression, and longer treadmill times (84).

**National Cooperative Study Group: Unstable Angina**

Under the auspices of the National Heart, Lung, and Blood Institute, a prospective, randomized study was initiated comparing intensive medical therapy with urgent coronary arterial bypass for the management of patients with unstable angina. Between 1972 and 1976, 288 patients were entered into the study (147 medical, 141 surgical). Eighty-two percent were men. All enrollees were under the age of 70 years. The patients had to have angina associated with transient ST-segment or T-wave changes on electrocardiogram. Ninety percent of the patients had rest pain while in the hospital. Although the patients had to have greater than 70% occlusion of at least one coronary artery to be eligible for randomization, 76% had multivessel CAD. Thirty percent of the individuals in the study had proximal left anterior descending arterial disease. Thus, the group corresponded to patients with Type II symptoms in the VA unstable angina study. Ejection fractions of 30% or less or greater than 50% narrowing of the left main coronary artery were reasons for exclusion as were an MI within three months or serious illnesses other than CAD.
At 65 months, there was no significant difference in survival between surgical and medical patients (85% surgery vs. 84% medical). Forty-three percent of patients crossed over from medicine to surgery (34% of those in NYHA classes I and II and 60% of those in NYHA classes III and IV). Crossover occurred sooner in patients with more severe angina (85).

As was the case in the other randomized studies, quality of life was better in the surgical group. At the end of the first year, severe angina was significantly more common in the medical group in patients with one-vessel disease \( (p < 0.05) \), two-vessel disease \( (p < 0.01) \), and three-vessel disease \( (p < 0.01) \). There was no significant difference in the incidence of nonfatal MI between the two treatment groups (86).

**Emory Angioplasty Versus Surgery Trial**

The Emory Angioplasty versus Surgery Trial (EAST) study was designed to determine whether initial revascularization with angioplasty in patients with multivessel coronary disease was a viable alternative to bypass surgery on the basis of outcome at three years. Between 1987 and 1990, 5118 patients were screened. Exclusion criteria included left main disease, two or more total occlusions of the coronary vessels, an ejection fraction less than or equal to 25%, recent MI (within five days), insufficient symptoms, and life-threatening noncardiac illnesses. Advanced age was not a criterion. Three hundred and ninety-two patients were randomized, 198 to PTCA and 194 to CABG. All had two- or three-vessel disease. The mean age of the PTCA patients was 61.8 years. The mean age of the CABG patients was 61.4 years; 74.7% of the PTCA patients and 72.7% of the CABG patients were men. Data were analyzed according to intention to treat.

OM was 1% in both groups. In-hospital Q-wave MIs were suffered by 10.3% of CABG patients and 3.0% of PTCA patients. Ten percent of the PTCA patients required CABG at the time of initial revascularization.

Within three years 6.2% of the CABG group had died compared with 7.1% of the PTCA group \( (p = 0.72) \). 19.6% of the CABG patients had suffered a Q-wave MI compared with 14.6% of those treated by PTCA \( (p = 0.21) \). During the three-year follow-up, 1% of the CABG group and 22% of the PTCA group required CABG. Thirteen percent of the CABG group and 41% of the PTCA group required PTCA. In terms of quality of life, the CABG group had a better outcome than the PTCA patients. Twenty percent of those treated by PTCA were in Canadian Cardiovascular Society classes II, III, or IV compared with 12% of those treated by CABG \( (p = 0.039) \). Sixty-six percent of the PTCA group and 51% of the CABG group required antianginal medication \( (p = 0.005) \).

Median initial procedure costs (in 1987) for PTCA were $14,166 compared with $22,894 for CABG. At three years, the median costs for treating a PTCA patient totaled $19,059; those for a CABG patient totaled $23,572. Procedure costs included physician and hospital costs (87,88).

**The Bypass Angioplasty Revascularization Investigation**

In 1987 the National Heart, Lung, and Blood Institute initiated the Bypass Angioplasty Revascularization Investigation (BARI) study to test the hypothesis that, during a five-year follow-up period, PTCA does not result in a poorer clinical outcome than does CABG in patients with multivessel coronary disease and severe angina or myocardial ischemia. Between 1988 and 1991, 1829 patients were randomized: 914 to CABG and 915 to PTCA. Mean age of the CABG patients was 61.1 years. That of the PTCA patients
was 61.8 years. Seventy-three percent of the PTCA patients and 74% of the CABG patients were men. Data were analyzed according to the intention-to-treat principle.

OM was 1.3% in the CABG group and 1.1% in the PTCA group; 4.6% of the CABG group and 2.1% of the PTCA group suffered a Q-wave MI ($p = 0.004$). Of all patients assigned to PTCA, 12.8% had additional revascularization procedures during the initial hospitalization; 6.3% of the PTCA patients required emergency CABG.

Cumulative survival rates at five years were 89.3% for CABG patients and 86.3% for PTCA patients ($p = 0.19$). Rates of survival free of Q-wave infarction at five years were 80.4% for those treated by CABG and 78.7% for those treated by PTCA ($p = 0.84$). Cumulative rates of Q-wave infarction at five years were 11.7% for CABG and 10.9% for PTCA ($p = 0.45$). During the five-year follow-up, 54.5% of the PTCA patients required revascularization procedures compared with 8.0% of the CABG patients. Nineteen percent of the PTCA group required multiple revascularization procedures compared with 3.0% of the CABG group. Improvement in functional status (as measured by the Duke Activity Scale) was better in the CABG patients (5.6 units vs. 3.2 units; $p = 0.04$).

Mean initial procedure cost for PTCA was $21,113 compared with $32,347 for CABG. At five years, the total mean costs for PTCA were $56,225 compared with $58,889 for CABG.

A major finding in this study was the difference in survival at five years between treated diabetics assigned to PTCA and treated diabetics assigned to CABG (65.5% for PTCA patients vs. 80.6% for CABG patients; $p = 0.003$). The term treated diabetics referred to those requiring insulin or oral hypoglycemic agents. As is true in most studies, the overall survival at five years for diabetics was less than that for nondiabetics (73.1% vs. 91.3%) (12,88,89).

Overview

While the general goal of each of the randomized trials summarized above was to compare the results of medical and surgical treatment of coronary arterial disease, it is clear that the individual studies differed substantially in mortality data, study design, patient selection, and patient recruitment. It is nevertheless striking that there are a number of major conclusions for which there is substantial agreement among the studies.

1. Angina pectoris is not in itself an indication for CABG except for the quality of life.
2. Surgical treatment for this purpose had a significant advantage in each of the trials.
3. CABG does not increase survival over that obtained by medical therapy for one- or two-vessel disease unless the patient falls into a high-risk category.
4. CABG has a clear advantage over medical management in the treatment of significant left main disease.
5. CABG results in a significantly increased survival when compared with medical management in patients with three-vessel disease and abnormal left ventricular function.
6. CABG results in better survival than medical management in patients who are high risk by clinical or angiographic criteria, or a combination of both.
7. Quality of life is uniformly better in the group treated by CABG. Exercise tolerance and freedom from angina are better in the surgical group. Requirements for medication and new hospitalizations for cardiovascular events are less in the surgical group.
8. In those groups that benefited from CABG, the benefits, particularly as they concern quality of life, tend to decrease with time. Even so, the advantages of CABG continue for 5 to 10 years.
When analyzed on the basis of intent-to-treat, there is no difference in three- to five-year survival of patients randomized to PTCA or CABG as the initial treatment for multivessel disease.

Over a three- to five-year period, there is no difference in the rate of Q-wave infarctions in patients initially randomized to PTCA or CABG.

Patients undergoing PTCA as the initial treatment for multivessel disease require additional revascularization procedures much more frequently than those initially treated by CABG.

Initial costs of PTCA are lower than those of CABG, but at five years the total costs are about equal.

Diabetics requiring insulin or oral hypoglycemic agents fare better with CABG than PTCA for multivessel CAD.

THE ELDERLY AS CANDIDATES FOR CABG

The five randomized studies comparing CABG with medical treatment were conducted in the 1970s in a younger, primarily male population. Mean ages in the five studies varied from 50 to 56 years. Patient outcomes in that group were used to determine indications for surgery. The current population undergoing CABG, however, has a different composition. It is older (mean age 65 years) and has a larger percentage of women (30%). Reports of outcomes following CABG in 70-, 80-, and even 90-year-olds are easily found in the literature but determining the benefits of CABG in this group and establishing indications for operation in the elderly necessarily involves an appreciation of the nature and extent of CAD in the patient population at risk. Table 8 compares by

| Baseline Characteristics of Patients Undergoing Cardiac Catheterization for Ischemic Heart Disease 1/1/95 Through 12/31/98 (21,573 Patients) |
| --- | --- | --- |
| Number of patients | <70 yr | 70–79 yr | >80 yr |
| Female gender | 26.0 | 36.4 | 44.2 |
| Severity of disease | | | |
| Left main disease | 6.3 | 11.3 | 13.9 |
| Three-vessel disease | 18.1 | 22.9 | 24.3 |
| 30%< EF <50% | 20.5 | 23.4 | 22.2 |
| Clinical indication | | | |
| Myocardial infarction | 27.1 | 25.5 | 31.8 |
| Unstable angina | 28.4 | 34.0 | 37.8 |
| Stable angina | 32.1 | 29.7 | 21.3 |
| Complications CAD | | | |
| Prior myocard infarction | 49.5 | 53.5 | 59.1 |
| Hx congest heart failure | 10.5 | 20.3 | 30.5 |
| Comorbidity | | | |
| Diabetes mellitus | 17.4 | 20.4 | 18.4 |
| Cerebrovascular disease | 4.2 | 8.7 | 11.5 |
| Peripheral vascular disease | 5.7 | 8.8 | 11.7 |
| Chronic pulmonary disease | 7.3 | 12.4 | 13.5 |
| Hypertension | 48.8 | 56.9 | 57.7 |

Abbreviations: CAD, coronary artery disease; EF, ejection fraction.
Source: From Ref. 90.
The prevalence of angina pectoris in the general population in the United States is approximately 1%. Prevalence increases with increasing age, afflicting 9.2% of a general population 55 to 69 years old and 14.7% of a general population 70 to 88 years old ($p = 0.0002$) (53). Even so, the prevalence of ischemic heart disease increases more rapidly with age than angina (3), indicating that CAD in the elderly is more likely to be present with manifestations other than uncomplicated angina.

Silent ischemia affects about 30% of the population over 70 years of age in contrast to 10% of a population in its 50s (25,26,91–94). Silent ischemia is not a benign event, even in the middle aged, but it is much more dangerous in the elderly. In Erikssen and Thaulow’s study of younger patients (91), there was 0.5% incidence of sudden death. Cardiac events occurred in 21–46% of younger patients with silent ischemia (92). In a study by Aronow (95), the prevalence of sudden death and coronary events in octogenarians was 38% and 69%, respectively, during 43 months of follow-up.

MI is not only more common in the elderly, but also it often goes unrecognized (39% of those over 65 vs. 27% of those under 65) (96,97). Dyspnea rather than chest pain becomes the predominant symptom of an acute MI in those over the age of 80 (98,99). Compared with a younger population, the elderly also have a higher mortality after infarction (12–39% vs. 2.0–8.0%) and a higher incidence of complications secondary to the infarction (99,100).

CHF is more common in older individuals with an annual incidence rising from 2/1000 in men 45 to 64 years old to 8/1000 in those 65 to 74 years old, 14/1000 in those 75 to 84 years old, and 54/1000 in those 85 to 94 years old. Women over the age of 75 years have a similar or greater rate of incidence. Mortality from CHF in those aged between 65 and 94 years is 88% within six years (101).

The incidence of sudden death from CAD in a general population rises from 1.1/1000 in men 45 to 54 years old to 2.6/1000 in men 65 to 74 years old. In women, the respective incidences are 0.3/1000 and 1.2/1000. The percentage of coronary attacks (death and/or MI) whose initial manifestation is sudden death increases from 13.6% in men 35 to 44 years old to 20% in men over 65 years old. The probability of sudden death also increases with the duration of uncomplicated angina (2.6% at two years; 9.7% at seven years). Males who have heart disease and are hypertensive, diabetic, and cigarette smokers represent an identifiable group who are at high risk for sudden death. The risk of sudden death over the age of 65 years is three to four times higher in men with CAD and two to seven times higher in women with CAD than it is in those without CAD (102,103).
OUTCOME

Effectiveness of CABG in the elderly must be measured against the results of alternative treatments such as PTCA, maximal medical management, or routine symptomatic treatment. When costs are being compared, expenses of treatment over a period of years must be considered rather than just those of the initial episode. Mortality and morbidity are the obvious short-term measurements to be made. The critical long-term measurements are survival and quality of life. Survival must not only be measured against that of the general population of similar age, but against the projected survival of a population in which CAD was allowed to pursue its natural course. Quality of life includes measurements such as relief of symptoms, freedom from further coronary events, and improvement in functional capacity. Costs are of concern to patients, their families, and society as both a practical matter and a philosophical issue.

Baseline Data

Table 10 depicts both expected survivals for a general population age 60 years in 1940 and for individuals in a general population of selected ages in 1992. The same table also depicts the expected survivals of patients with angina pectoris prior to the advent of modern medical and surgical treatment. The data reported by White (48) and Block (50) excludes patients with valvular disease, but includes some patients with a history of MI, CHF, hypertension, and diabetes. The data reported by Kannel (45) represents survivals of patients with uncomplicated angina pectoris; that is, patients without valvular disease, MI, or the coronary insufficiency syndrome. While the data from White and Block are older (30s and 40s) than those from Kannel, the composition of their patient populations more closely approximates that of current populations undergoing CABG. The two sets of data represent the extremes of outcome against which the results of medical and surgical treatment can be evaluated.

### Table 9  Characteristics of Patients Undergoing Coronary Bypass Grafting: Comparison of Those Aged Less Than 70 years with Those Aged 70 Years and Older

<table>
<thead>
<tr>
<th>Factor</th>
<th>Under 70 yr</th>
<th>70 yr or Older</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Range Mean</td>
<td>Range Mean</td>
</tr>
<tr>
<td>Female gender</td>
<td>13.0–38.7 28.3</td>
<td>24.6–46.0 27.8</td>
</tr>
<tr>
<td>NYHA IV</td>
<td>23.0–56.0 44.8</td>
<td>20.0–63.0 36.7</td>
</tr>
<tr>
<td>Left main disease</td>
<td>7.0–20.9 13.1</td>
<td>3.4–35.0 16.4</td>
</tr>
<tr>
<td>Three-vessel disease</td>
<td>40.8–78.0 49.0</td>
<td>27.0–90.0 61.9</td>
</tr>
<tr>
<td>30% &lt; EF &lt; 50%</td>
<td>19.7–42.0 24.6</td>
<td>22.0–66.0 33.3</td>
</tr>
<tr>
<td>Prior myocardial infarction</td>
<td>35.0–62.0 57.4</td>
<td>22.8–68.5 53.6</td>
</tr>
<tr>
<td>Hx congestive heart failure</td>
<td>3.0–33.6 9.7</td>
<td>7.0–67.0 17.1</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>4.0–28.0 16.1</td>
<td>3.0–60.0 12.6</td>
</tr>
<tr>
<td>Cerebrovascular disease</td>
<td>– 6.0</td>
<td>6.4–21.0 9.0</td>
</tr>
<tr>
<td>Peripheral vascular disease</td>
<td>4.4–13.0 4.4</td>
<td>4.2–26.0 5.4</td>
</tr>
<tr>
<td>Urgent or emergent surgery</td>
<td>6.0–41.0 9.5</td>
<td>7.0–56.8 17.3</td>
</tr>
</tbody>
</table>

**Abbreviations:** NYHA, New York Heart Association; EF, ejection fraction; Hx, History.
<table>
<thead>
<tr>
<th>Source</th>
<th>Reference year</th>
<th>Age of population</th>
<th>Nature of population</th>
<th>1</th>
<th>5</th>
<th>10</th>
<th>15</th>
<th>20</th>
</tr>
</thead>
<tbody>
<tr>
<td>Life Tables US</td>
<td>1940</td>
<td>60</td>
<td>General population</td>
<td>98.2</td>
<td>87.6</td>
<td>72.0</td>
<td>53.3</td>
<td>33.2</td>
</tr>
<tr>
<td>Life Tables US</td>
<td>1992</td>
<td>50</td>
<td>General population</td>
<td>99.5</td>
<td>97.2</td>
<td>92.9</td>
<td>86.6</td>
<td>77.9</td>
</tr>
<tr>
<td>Life Tables US</td>
<td>1992</td>
<td>60</td>
<td>General population</td>
<td>98.8</td>
<td>93.2</td>
<td>83.8</td>
<td>71.5</td>
<td>56.4</td>
</tr>
<tr>
<td>Life Tables US</td>
<td>1992</td>
<td>70</td>
<td>General population</td>
<td>97.3</td>
<td>85.3</td>
<td>67.2</td>
<td>46.1</td>
<td>—</td>
</tr>
<tr>
<td>Life Tables US</td>
<td>1992</td>
<td>80</td>
<td>General population</td>
<td>94.0</td>
<td>68.5</td>
<td>—</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>Life Tables US</td>
<td>1992</td>
<td>80–89</td>
<td>General population</td>
<td>92.0</td>
<td>62.0</td>
<td>—</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>White, Bland</td>
<td>1931</td>
<td>56.5</td>
<td>Natural Hx angina pectoris</td>
<td>89.3</td>
<td>64.2</td>
<td>39.8</td>
<td>19.5</td>
<td>12.7</td>
</tr>
<tr>
<td>Block</td>
<td>1927–1944</td>
<td>58.8</td>
<td>Natural Hx angina pectoris</td>
<td>84.7</td>
<td>58.4</td>
<td>37.1</td>
<td>22.1</td>
<td>14.1</td>
</tr>
<tr>
<td>Kannel</td>
<td>1949–1952</td>
<td>≥50, men</td>
<td>Natural Hx uncomplicated AP</td>
<td>100</td>
<td>84.0</td>
<td>58.0</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>Barzilay</td>
<td>1944</td>
<td>68</td>
<td>ND+CAD</td>
<td>—</td>
<td>75.0</td>
<td>55.0</td>
<td>34.0</td>
<td>—</td>
</tr>
<tr>
<td>Barzilay</td>
<td>1944</td>
<td>68</td>
<td>DM+CAD</td>
<td>—</td>
<td>63.0</td>
<td>39.0</td>
<td>21.0</td>
<td>—</td>
</tr>
</tbody>
</table>

**Percentage survival at specified intervals (yr)**

**Abbreviations:** CAD, coronary artery disease; ND+CAD, nondiabetic patient with CAD treated either medically or surgically; DM+CAD, diabetic patient with CAD treated either medically or surgically; Uncomplicated AP, angina pectoris uncomplicated by myocardial infarction, coronary insufficiency, or coronary death.
Operative Mortality

Reported OM following CABG in the elderly varies widely as a result of differences in patient selection. Advanced cardiac disease, high prevalence of associated diseases, and the need for urgent or emergency operation are the major factors that increase mortality in the elderly. Table 11 (104–110) is a composite of operative mortalities reported in various age groups undergoing elective or emergency operation. It is apparent that OM increases with advancing age and the priority of the procedure. Performing CABG urgently or emergently in the elderly is associated with a very high OM. Table 12, a compilation of data from Curtis et al. (106), Peterson et al. (107), and He et al. (111), lists the effects of selected factors on OM following CABG in the elderly. Again, performing CABG as an urgent or emergency procedure clearly has the greatest adverse effect on OM. Dziuban (112), describing his group’s experience with 460 patients, found an OM of 1.2% following elective CABG; 3.2% after urgent CABG, and 26% if the operation was performed as an emergency. In series in which the adverse factors listed in Table 12 were not significantly higher in elderly patients, operative mortalities of 1.0–1.3% were reported in groups of patients with a mean age of 61 and 1.0–4.2% in those aged 70 and above (13,89,108,113). DM treated with insulin or oral hypoglycemic agents is associated with an increased 30-day mortality following CABG. Carson (114), reporting outcomes in 146,786 patients with a mean age of 65 years, found that OM in those without DM was 2.7%. Thirty-day OM with DM controlled by oral medications was 3.2% while OM in insulin-dependent diabetics was 4.6%.

Table 11  Summary of Reported Operative Mortality Following Coronary Artery Bypass by Age Groups

<table>
<thead>
<tr>
<th>Priority of operation</th>
<th>≤50</th>
<th>&lt;70</th>
<th>≥70</th>
<th>≥80</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overall</td>
<td>0.6–3.0</td>
<td>1.0–5.2</td>
<td>1.8–12.0</td>
<td>2.0–24.0</td>
</tr>
<tr>
<td>Elective</td>
<td>0.4–0.7</td>
<td>0.6–1.6</td>
<td>1.0–4.2</td>
<td>0.0–8.0</td>
</tr>
<tr>
<td>Urgent or emergent</td>
<td>2.2–4.8</td>
<td>4.9–5.1</td>
<td>4.1–22.2</td>
<td>8.8–28.6</td>
</tr>
</tbody>
</table>

Table 12  Relative Effects of Selected Factors on 30-Day and 3-Year Mortality

<table>
<thead>
<tr>
<th>Factor</th>
<th>Relative mortality</th>
</tr>
</thead>
<tbody>
<tr>
<td>Urgent or emergent operation</td>
<td>4.50</td>
</tr>
<tr>
<td>Cigarette smoking</td>
<td>2.69</td>
</tr>
<tr>
<td>Chronic renal failure</td>
<td>2.42</td>
</tr>
<tr>
<td>Hx myocardial infarction</td>
<td>2.33</td>
</tr>
<tr>
<td>Cerebrovascular disease</td>
<td>2.22</td>
</tr>
<tr>
<td>Congestive heart failure</td>
<td>1.77</td>
</tr>
<tr>
<td>Peripheral vascular disease</td>
<td>1.42</td>
</tr>
<tr>
<td>Age</td>
<td>1.37–3.50</td>
</tr>
<tr>
<td>Female gender</td>
<td>1.19–2.90</td>
</tr>
<tr>
<td>Pulmonary disease</td>
<td>0.96</td>
</tr>
</tbody>
</table>

Abbreviation: Hx, history.
Morbidity After CABG

Overall postoperative morbidity in the elderly can be as high as 65%. Nineteen percent of the complications are life threatening, while 30% of patients have two or more complications (115). Table 13 summarizes morbidity following CABG (108–110,116–124). It is apparent that the overall frequency of complications increases with age over 70 years. The most common minor complications over age 70 were cardiac arrhythmias. Atrial fibrillation occurred in 10–40% of patients (109,113,125). Major complications were suffered by 22–24% of those older than 70 years (120,125). The most common major complications were MI, pneumonia, and stroke. Carson (114), reporting morbidity, infection, and septicemia rates in 146,786 CABG patients with an average age of 65 years, noted that the risk of infection and other serious life-threatening complications was 36–38% higher in diabetics treated with insulin or oral agents even after adjusting for differences in risk factors.

Survival

Table 14 summarizes survival data from several authors (90,110,113,117,118,121,126–128). Again, there is some variation as a result of patient selection, but it is clear that long-term survival following CABG of those aged 70 years or older as well as those in their 80s closely approximates that of a general population of like age (Table 10). It is also clear that survival of patients after CABG is markedly better than would have been the case if the angina had been allowed to pursue its natural course (Table 10). Although most authors have reported a higher OM in women, long-term survival of women following CABG is at least as good as that of men in all age groups (116) (Table 15).

Increasing age, ejection fraction below 35%, severe wall motion abnormalities, end-systolic volume greater than 80 mL, and the presence of two or more associated medical conditions are predictors of decreased long-term survival (126,129). Over age 65 years, 45% of late deaths are due to noncardiac causes. Below age 65 years, 29% of late deaths are due to noncardiac causes. Diabetics with CAD, particularly those requiring insulin or oral hypoglycemic agents, have a decreased long-term survival regardless of the method...
of treatment of their CAD. However, their survival is better with CABG than it is with either PTCA or medical management (89,130–134) (Table 16).

Table 17 summarizes survival data following PTCA (87,88,117,131,135). Immediate mortality following PTCA in the elderly is consistently lower than that following CABG. In controlled studies, five-year survival following PTCA closely approximates that following CABG (except for therapeutic drug monitoring) (88,89,135).

Table 18 compares long-term survival following medical treatment of CAD with that following CABG in the elderly (110,127). Although it is probable that, in these nonrandomized studies, patients treated medically were sicker than those treated surgically, the data that are available strongly suggest that elderly patients who undergo CABG fare better than their medical counterparts in terms of prolonged survival, relief of symptoms, and restoration of an active lifestyle. Cumulative six-year survivals of 1491 patients aged 65 years or older in the Coronary Artery Surgery Study (CASS) were 80% in the surgical group and 63% in the medical group (127). Ko et al. (110) reported in 1992
Surgical Management of CAD in the Elderly

Table 16  Reported Survivals of Diabetes with CAD by Author, by Year, and by Duration (Various Modes of Therapy)

<table>
<thead>
<tr>
<th>Reference (yr)</th>
<th>Mean age (yr)</th>
<th>Study</th>
<th>1 yr</th>
<th>3 yr</th>
<th>5 yr</th>
<th>7 yr</th>
<th>10 yr</th>
<th>15 yr</th>
</tr>
</thead>
<tbody>
<tr>
<td>130 (1994)</td>
<td>68</td>
<td>DM + CABG</td>
<td>72</td>
<td>48</td>
<td>24</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>DM + MED</td>
<td>50</td>
<td>24</td>
<td>18</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>132 (1991)</td>
<td>82</td>
<td>ND + CABG</td>
<td>88</td>
<td>83</td>
<td>64</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>DM + CABG</td>
<td>65</td>
<td>—</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>133 (1993)</td>
<td>59</td>
<td>ND + CABG</td>
<td>98</td>
<td>96</td>
<td>94</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>DM + CABG</td>
<td>96</td>
<td>89</td>
<td>81</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>134 (1991)</td>
<td>55</td>
<td>ND + CABG</td>
<td>95</td>
<td>93</td>
<td>91</td>
<td>86</td>
<td>76</td>
<td>64</td>
</tr>
<tr>
<td></td>
<td></td>
<td>DM + CABG</td>
<td>92</td>
<td>88</td>
<td>85</td>
<td>74</td>
<td>63</td>
<td>41</td>
</tr>
<tr>
<td>89 (1997)</td>
<td>62</td>
<td>TDM + CABG</td>
<td>81</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>TDM + PTCA</td>
<td>66</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>131 (1996)</td>
<td>57</td>
<td>ND + PTCA</td>
<td>97</td>
<td>95</td>
<td>92</td>
<td>87</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>60</td>
<td>DM + PTCA</td>
<td>93</td>
<td>90</td>
<td>82</td>
<td>74</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Abbreviations: ND, nondiabetic; DM, diabetic; TDM, diabetic patients requiring insulin or oral hypoglycemic agents; +CABG, treated by coronary artery bypass; +PTCA, treated by balloon angioplasty.

Table 17  Reported Survivals Following PTCA or CABG by Author, by Year, by Duration, and by Treatment

<table>
<thead>
<tr>
<th>Reference (yr)</th>
<th>Mean age (yr)</th>
<th>Study</th>
<th>1 yr</th>
<th>3 yr</th>
<th>5 yr</th>
<th>7 yr</th>
<th>9–10 yr</th>
</tr>
</thead>
<tbody>
<tr>
<td>131 (1996)</td>
<td>57</td>
<td>ND + PTCA</td>
<td>97.9</td>
<td>95.0</td>
<td>91.6</td>
<td>86.6</td>
<td>82.3</td>
</tr>
<tr>
<td></td>
<td>60</td>
<td>DM + PTCA</td>
<td>92.8</td>
<td>89.5</td>
<td>81.5</td>
<td>74.1</td>
<td>64.1</td>
</tr>
<tr>
<td>87 (1994)</td>
<td>62</td>
<td>PTCA</td>
<td>96.5</td>
<td>92.9</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>61</td>
<td>CABG</td>
<td>97.9</td>
<td>93.8</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>88 (1996)</td>
<td>62</td>
<td>PTCA</td>
<td>96.5</td>
<td>91.8</td>
<td>86.3</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>61</td>
<td>CABG</td>
<td>96.5</td>
<td>93.8</td>
<td>89.3</td>
<td></td>
<td></td>
</tr>
<tr>
<td>89 (1997)</td>
<td>62</td>
<td>ND* + PTCA</td>
<td>90.5</td>
<td></td>
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<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>ND* + CABG</td>
<td>89.7</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>135 (1994)</td>
<td>75</td>
<td>PTCA</td>
<td>87.5</td>
<td>77.5</td>
<td>63.0</td>
<td></td>
<td></td>
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<tr>
<td>75</td>
<td>CABG</td>
<td>85.0</td>
<td>72.5</td>
<td>65.0</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>117 (1994)</td>
<td>84</td>
<td>PTCA</td>
<td>88.0</td>
<td>83.0</td>
<td>55.0</td>
<td>21.0</td>
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<tr>
<td>82</td>
<td></td>
<td></td>
<td>89.0</td>
<td>77.0</td>
<td>66.0</td>
<td>42.0</td>
<td></td>
</tr>
</tbody>
</table>

Abbreviations: ND, nondiabetic; PTCA, percutaneous transluminal coronary angioplasty; CABG, coronary artery bypass graft; ND*, nondiabetic and diabetics not requiring insulin or oral hypoglycemic agents.

that octogenarians treated by CABG had a better three-year survival than those treated medically (77.2% vs. 55.2%). Peterson (107), describing Medicare data, noted that one-year survival was 92.1% after CABG in 147,822 individuals, 65 to 70 years old. Three-year survival was 86.9%. One- and three-year survivals were 80.9% and 71.2% in 24,461 patients aged 80 years and older. Graham (90), reviewing data from the Alberta, Canada registry, reported that patients in three age groups had better four-year survival following CABG than they did following medical management (Table 19). In that study, those over 80 years of age benefited most from CABG. Procedural mortality was not reported.
Quality of Life

As survival following treatment of ischemic heart disease has improved, measurement of the quality of the patient’s life following treatment has become a focus of increasing discussion. Evaluation of OM, morbidity, and survival are readily addressed by objective measurements, but quality of life is less easily measured objectively. Investigators often use indirect measurements such as freedom from cardiac events, relief of pain, decreased requirements for medication, or fewer hospitalizations as evidence of a better quality of life. Attempts to develop objective direct measurements have involved use of instruments such as the Duke activity score index, the SF 36 health survey, the Rose questionnaire for angina, the Hospital Anxiety and Depression scale, the Nottingham Health Profile, the EuroQol Questionnaire, and changes in the NYHA or the Canadian Cardiac Society classification (136–138). Each requires patient’s self-assessment as well as the patient’s understanding of the questions, ability, and willingness to respond. Nevertheless, there is substantial data to indicate that both medical and surgical treatment improve the quality of patients’ lives.

Freedom from Events

Multiple authors have reported that at five years, 59–78% of elderly patients surviving CABG; 40–70% of those surviving PTCA; and 67% of those treated medically for CAD...
were free of recurrent cardiac events (128,135,139,140). The term “cardiac events” usually included death or new Q-wave infarction, but in some publications it also included reoperation, arrhythmia, and stroke.

**Freedom from Angina**

Severe intractable angina is the most frequent indication for CABG in the elderly. After CABG, 62–94% of patients were found to be free of angina with follow-up ranging from three months to eight years (12,110,118,122,127,135,140,141). Fifty-five percent to 82% of elderly patients treated by PTCA and 29–51% of those treated medically were free of angina (12,87,118,127,135,140,142). Vogt (142) reported that 85% of elderly patients treated by CABG were free of angina 6 to 12 months later compared with 55% of those treated by PTCA and 51% of those managed medically. In general, PTCA and medically treated patients were more likely to be taking antianginal medications than were the CABG patients. The advantages of surgical treatment over medical treatment seem to decrease slowly over time but were sustained for at least 10 years (141).

**Posttreatment MI**

The frequency of recurrent or late MI one to five years after CABG in the elderly ranged from 0% to 2%. Following PTCA, the frequency was 2–6%. After medical management, the frequency of a new MI was as high as 28% (122,135,143).

**Functional Status**

In terms of mobility, ability to care for themselves or live independently, the elderly clearly benefit more from CABG than from medical management. When the high frequency of CABG following PTCA is considered, patients treated only by CABG probably have a better quality of life than do those treated only by PTCA.

Ko (110) reported that CABG produced a significant improvement in functional capacity lowering the NYHA classification from an average of 3.4 preoperatively to 1.2 postoperatively. Medical management did not (2.8 to 2.5). Similarly, Mullany (118) found that 89% of the elderly undergoing CABG were returned to NYHA class I or II. Preoperatively, 97% of the patients were NYHA class III or IV. Krumholz (143), evaluating 93 octogenarians following hospitalization for an acute MI, found that one year later, 89% of those treated by CABG, 86% of those treated by PTCA, and 44% of those treated medically rated their quality of life as good or excellent. King (87) reported that 44.5% of patients treated by CABG and 47% of those treated by PTCA were able to engage in moderate or strenuous activity.

Akins (128) commented that 86% of octogenarians who had undergone CABG were living at home or with their families. Krumholz et al. (143) found that 89% of octogenarians treated by CABG, 89% of those undergoing PTCA, and 55% of those treated medically for CAD were living independently. For comparison, earlier in this chapter the comment was made that half of the general population 85 years or older still lived alone or with their spouses (21).

Several authors have attempted to measure quality of life objectively. Vogt (142), measuring outcomes in 98 individuals older than 70 years, found that patients undergoing CABG were significantly more able to engage in the basic and intermediate activities of daily living than were those who underwent PTCA or medical therapy. Hlatky et al. (12) measured functional status following CABG or PTCA in a group of 934 patients with a mean age of 62 years. Employing the Duke Activity Status Index, he reported that
improvement was significantly better after CABG than after PTCA (7.0 vs. 4.4). Chocron et al. (141), using the Nottingham Health Profile, found that three months after CABG, 92% of elderly patients reported improvement in their social activities, 89% in their energy, 80% in their physical mobility, and 79% in their pain. Speziale et al. (144), using a questionnaire that evaluated five areas of activity, reported the results at three years from 203 patients treated by CABG, 107 patients treated medically, and 107 normal patients. Mean age was 60 years. The surgical patients scored significantly better than the medical patients, but both treatment groups scored significantly worse than the normals.

COSTS

From the data presented, it is apparent that CABG and/or PTCA cannot only extend the life of elderly patients with CAD, but also they can prevent further myocardial injury, restore function, and increase the quality of life. Costs, however, are a valid consideration as these procedures are performed in increasing numbers of the elderly. Peterson et al. (107) noted that the rate of CABGs performed in those aged 65 to 70 grew from 38.1/10,000/yr in 1987 to 42.1/10,000/yr in 1990. The rate in octogenarians grew from 7.2/10,000/yr in 1987 to 12.0/10,000/yr in 1990. The total number of bypass operations performed in octogenarians is expected to increase from 8000 in 1990 to more than 30,000 by 2050 at an in-hospital cost that will exceed $1.2 billion in 1990. In 1990, the mean hospital cost for a CABG performed in patients 65 to 70 years old was $21,700; for those in their 80s the mean cost was $27,200 (107).

The increased costs for CABG in the elderly result primarily from longer hospital stays and more intensive treatment rather than from the procedure itself. In turn, the prolonged stays are due to the presence and severity of coexisting disease, the generally more advanced stage of CAD at the time of operation, and the increased frequency of postoperative complications in the elderly.

Smith et al. (145), reviewing economic outcomes in 1114 patients undergoing CABG, found that lower ejection fractions, higher age, CHF, presence of unstable angina, cardiomegaly, stroke, renal disease, and diabetes requiring insulin were significant patient factors that predicted higher costs. Lower age, higher ejection fractions, absence of diabetes, no prior PTCA, and male sex predicted earlier hospital discharge.

Comparative costs of PTCA and CABG are also valid considerations. It is generally accepted that the initial costs for PTCA are significantly less than the costs of CABG (35–84% less) (12). Over a period of time, however, the total cost of PTCA approaches that of CABG because of more frequent hospitalizations, more frequent revascularization procedures, and a greater cost for medications. Hlatky (12) concluded that over a three- to five-year period, balloon angioplasty has a significant cost advantage over CABG in patients with two-vessel disease. In patients with three-vessel disease, the costs were similar. In diabetics with CAD, bypass surgery was more cost-effective than angioplasty.

As the number of cardiac revascularization procedures performed in progressively older patients continues to increase and the cost of health care continues to escalate, the question of cost-effectiveness of these procedures in the elderly has become a topic of discussion among health planners. The TIME investigators (Switzerland) (136) noted that individuals older than 75 years represent the fastest growing segment of the population. They pointed out that more than one-third of the total health care expenditures are consumed by this group of individuals in whom coronary artery disease is the most prominent cause of morbidity and mortality. Sollano (138) studied the cost-effectiveness of CABG surgery versus medical management in 224 patients 80 years of age or older.
Survival and quality of life were evaluated posttreatment. Cost per quality-adjusted life-years saved was calculated. In the group undergoing CABG the cost per year was $10,424, well within the benchmark of $50,000 per year considered to be cost-effective for a number of other treatments. They concluded that performance of CABG surgery in octogenarians was highly cost-effective.

RECENT DATA

The Society of Thoracic Surgeons National Database reviewed retrospectively 662,033 patients (five patients older than 100 years old, 1092 patients aged 90 to 99 years, 59,576 patients aged 80 to 89 years, and 621,360 patients aged 50 to 79 years) who underwent cardiac surgical procedures from 1997 through 2000 (146). For CABG patients, OM was 11.8% for patients aged 90 years and older, 7.1% for patients aged 80 to 89 years, and 2.8% for patients aged 50 to 79 years. Patients aged 90 years and older, who did not have emergent/salvage CABG, preoperative intra-aortic balloon, renal failure, peripheral vascular disease, or cerebrovascular disease had an OM of 7.2% (146).

In 500 consecutive patients aged 80 to 94 years who had CABG, revascularization was complete in 400 patients (80%) (147). OM was 7% in the 400 patients with complete revascularization and 13% in the 100 patients with incomplete revascularization. Excluding operative deaths, the mean survival was 82 months in patients with complete revascularization versus 65 months in patients with incomplete revascularization. The five-year survival was 62% in patients with complete revascularization versus 45% in patients with incomplete revascularization. The eight-year survival was 39% in patients with complete revascularization versus 25% in patients with incomplete revascularization (147).

A propensity analysis of long-term survival after CABG or PTCA in 6033 consecutive patients, mean age 65 years, with multivessel CAD and high-risk features showed that PTCA was associated with an increased risk of death (propensity-adjusted hazard ratio = 2.3) (148). This difference was observed across all categories of propensity for PTCA and in patients with DM or left ventricular dysfunction (148).

Cardiac rehabilitation programs can be used to optimize the recovery outcomes of elderly persons after CABG (149). Octogenarians undergoing CABG have better health status at four years than those in the same age group who did not undergo revascularization (150). Octogenarians with preoperative comorbidities such as DM, CHF, stroke, hypertension, carotid artery disease, and low left ventricular ejection fraction have an excellent quality of life after CABG (151).

In 4739 patients, mean age 67 years, undergoing CABG, multivariate analysis showed that preoperative use of lipid-lowering therapy reduced in-hospital mortality by 17% (153). In elderly high-risk patients, no significant difference was found in the incidence of cognitive dysfunction at three months with either off-pump CABG or with conventional CABG (152).

INDICATIONS FOR CABG IN THE ELDERLY

Compared with cardiac disease in the younger population, CAD in the elderly is more likely to be associated with severe complications and a higher mortality from those complications. Age, in itself, has been shown repeatedly to be an independent predictor of an increased OM. Thus, the elderly face greater risks in the perioperative period while at the same time the durability of long-term benefits is necessarily limited. Nevertheless,
conclusions drawn from the randomized studies together with data from multiple nonrandomized studies of coronary revascularization in the elderly have led to generally accepted indications for CABG in older patients. As summarized by Aronow (154), they are as follows:

1. Significant left main disease
2. Significant three-vessel disease, especially in the presence of a decreased left ventricular ejection fraction and ischemia
3. Significant two- or three-vessel disease, a decreased left ventricular ejection fraction, and significant stenosis of the proximal left anterior descending coronary artery
4. ST-segment depression on resting ECG plus at least two of the following—NYHA functional class III or IV, history of MI, history of hypertension, or all three without ECG changes
5. Significant two- or three-vessel disease and exercise-induced ischemic ST-segment depression of 1.5 mm or greater
6. Clinical evidence of CHF during ischemic episodes with ischemic but viable myocardium
7. Unacceptable symptoms despite optimal medical management.

Rihal et al. (155) performed a meta-analysis of trials comparing PTCA with CABG. These investigators found that PTCA was preferred for high-risk patients such as those with left main CAD, severe three-vessel CAD, diffuse CAD, severe left ventricular dysfunction, or DM. Both PTCA and CABG provided good symptom relief. However, repeat procedures are required more frequently after PTCA than after CABG (154).

SUMMARY

Coronary angioplasty or bypass is being performed for increasing numbers of patients in their seventh, eighth, ninth, and even tenth decades of life. Both silent and overt CAD are more common in the population over 65. Because CAD in the elderly presents more often in an atypical manner, diagnosis of the disease is frequently delayed. As a result, the elderly typically face the operation with a higher prevalence of complications of their CAD. MI, impaired myocardial function, and CHF are more frequent in the elderly. CABGs are performed more frequently as emergencies in older individuals, particularly those aged 80 years or older.

Nevertheless, it is clear from recent reports that elective CABG can be performed with operative mortalities in the 1.0–4.0% range even in 70- and 80-year-olds. Survival of the elderly treated by CABG approximates that of a general population of the same age group and is markedly superior to that achieved by medical management. It is also true that CABG in older individuals improves the quality of life over and above that observed following alternative methods of treatment, particularly medical management.

While the costs of performing CABG in the elderly are higher than they would be for a younger population, it is not clear that these costs are higher in the long run than they would be for nonoperative treatment with its associated costs of repeated interventions and hospitalizations.

Greater efforts directed toward detection of ischemic heart disease in the older population and performance of earlier, elective surgery could significantly reduce both the mortality and disability associated with CAD in the elderly. Delay in operation until the patient has a complication of CAD, particularly a MI, has a markedly adverse outcome in both the short and the long term.
REFERENCES


14
Percutaneous Coronary Intervention in the Elderly

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The numbers of older (age over 65 years) and oldest (those over age 80 years) patients with coronary artery disease (CAD) are increasing in our society at a tremendous rate. Indeed, there has been unsurpassed growth in the elderly population in the last 10 to 15 years. Within a decade, one-sixth of the population, representing 45 million people, will be over the age of 65 (1), with half of those being over the age 75 and some 25% of those over the age of 80. The elderly have a high prevalence (about 60%) of significant atherosclerotic CAD in at least one coronary vessel, with many becoming symptomatic enough to require definitive treatment (2). The increase in prevalence of CAD with increasing age is seen irrespective of gender status (3). Patients older than 65 now constitute over half of all patients undergoing coronary revascularization procedures at major medical centers (4–7).

Unfortunately, many studies of revascularization for symptomatic CAD in the past have either excluded patients over the age of 70 to 75 or have included insufficient number of patients to draw effective conclusions. There is a high proportion of more extensive disease, more frequent and more severe medical comorbidities, and poorer success rates leading to higher complication/death rates in the elderly, both with percutaneous coronary intervention (PCI) (7–9) as well as with coronary artery bypass surgery (CABG) (10). These factors make the decision to perform coronary revascularization challenging. With the rapid evolution of PCI techniques, one must continually reevaluate PCI’s applicability in the setting of older, sicker patients to better advise about its relative benefit versus alternative treatment strategies.

BASIS FOR INTERVENTION IN THE ELDERLY

Recent studies have shown that elderly patients with symptomatic CAD have poorer long-term and event-free survival with medical therapy alone compared with revascularization (11,12). The large observational Alberta Provincial Project for Outcomes Assessment in Coronary Heart Disease (APPROACH) study, set in the mid-1990s, (6000 patients with
CAD over age 70, about 1000 patients over age 80) noted age-related differences in adjusted four-year survival in the elderly with medical treatment (MED) compared with PCI and CABG as follows: aged below 70 years MED = 90.5%, PCI = 93.8%, CABG = 95%; aged 70 to 79 years MED = 79.1%, PCI = 83.9%, CABG = 87.3%; aged above 80 years MED = 60.3%, PCI = 71.6%, CABG = 77.4% (11). Elderly patients, in general, did poorer with medical therapy, and this trend seemed to worsen with increasing patient age. Graham et al. and other study groups (11,13) have shown the benefits of revascularization in carefully selected elderly patients are more pronounced. In addition to frequent symptoms, some 50% of medically treated patients will be admitted with an acute coronary event, a trend that can be favorably impacted with timely revascularization therapy (12).

Other factors in the elderly limit the overall utility of medications as a primary option for therapy; their ischemia is often refractory to medication, leading to the more frequent need to maximize medical therapy (14). Maximizing medical therapy with multiple medications can lead to multiple adverse drug-drug interactions. Elderly patients often have a substantial degree of medication intolerance (due to peptic ulcer disease/other gastrointestinal conditions among others), as well as cognitive impairment that can lead to poorer compliance with medications than younger patients (15–17). Maximizing medical therapy with multiple medications can lead to multiple adverse drug interactions. Elderly patients often have a substantial degree of medication intolerance (due to peptic ulcer disease/other gastrointestinal conditions among others), as well as cognitive impairment that can lead to poorer compliance with medications than younger patients (15–17). Undoubtedly, for a multitude of reasons, older patients tend to downplay their symptoms and delay seeking care; when they do present with active coronary ischemia, they are more likely to do so late, with signs of severe congestive heart failure (CHF), acute myocardial infarction, and/or cardiogenic shock (8,9). It is these very subsets of elderly who are shown to carry a poorer prognosis with medical therapy in the absence of revascularization (18,19). Together with a high prevalence of chronic symptomatic ischemia, a high burden of atherosclerosis, and many medical comorbidities, active CAD can be a tremendously disabling problem in the elderly, one that often prompts patients to consider the more definitive benefits offered by revascularization therapy.

The Trial of Invasive versus Medical Therapy in Elderly Patients (TIME) (12) randomized 301 elderly patients aged 75 years and above to either coronary angiography and revascularization or to further optimization of medical therapy. At baseline, three quarters of the patients had Canadian Cardiac Society (CCS) class III or IV angina pectoris despite using an average of 2.5 antianginal drugs. The primary endpoint was quality of life assessed at six months. Although angina severity decreased and quality of life improved in both groups, these improvements were significantly greater in the group of patients treated with revascularization. In the invasive group, 19% had a major adverse cardiac event at six months versus 49% in the medical group (p < 0.0001). The one-year follow up of the TIME trial in elderly patients has now been reported. Pfisterer et al. reported on 282 patients with CCS class II or higher angina who survived for the first six months after enrollment. The mean age was 80 years. At one year, there was no statistically significant difference in death [11.1% for invasive versus 8.1% for medical therapy; hazard ratio (HR) 1.51, 95%, confidence interval (CI) 0.72–3.16, p = 0.28] or the combined endpoint of death or nonfatal infarction (17% for the invasive group vs. 19.6% for the medical therapy group, HR 0.90, 95%, CI 0.51–1.53, p = 0.71). There was, however, a marked difference in subsequent revascularization. Patients randomized to medical therapy had a 46% chance of later hospitalization and revascularization versus 10% with an invasive approach (HR 0.17, 95%, CI 0.11–0.32, p < 0.001) (20). After four years, the patient survival was 70.6% in the invasive group versus 73% in the medically treated group (not significant). Survival rates were, however, better if patients were revascularized within the first year of study entry. At four years, freedom from major adverse cardiac event rate remained significantly higher in the invasive group (21).
Quality of life has also been assessed after coronary revascularization in the elderly. Graham et al. (22) evaluated four-year health status in elderly patients using the Seattle Angina Questionnaire. At four years of follow-up, health status was better in patients who had undergone revascularization as the index procedure compared with medical therapy. Finally, cost effectiveness has also been studied in the setting of the TIME trial. Costs were determined by resource utilization at one year. The two strategies had different cost profiles, with invasively treated patients having higher initial costs, but medically treated patients having higher subsequent costs. Accordingly, at one year, patients treated with an invasive strategy had improved clinical outcomes at only marginally higher costs (23).

CHARACTERISTICS OF THE ELDERLY PCI POPULATION

Elderly subjects undergoing PCI are generally sicker than younger ones because of a higher prevalence of comorbid medical conditions (7,23,24). Patients over age 65 frequently have hypertension and diabetes leading to more advanced CAD, peripheral vascular disease, and cerebrovascular diseases (6,23,24). In addition, older patients have a greater burden of coronary atherosclerosis associated with a relatively frequent history of PCIs and/or CABG, prior myocardial infarction, and resultant lower ejection fraction (EF) (6,14,23,25,26). On the basis of a multicenter registry study, CHF is common in the elderly and comparatively rare in younger patients; only 4% of patients younger than 65 have had CHF versus some 9% over 65 years and 20% over age 75 (14). This is true of both systolic and diastolic heart failure. In addition, there is a higher percentage of women undergoing PCI over age 75 (40–50%) compared with those younger than 65 (21%), a factor that alone shows a trend toward higher need for subsequent revascularization procedures (24).

The presence of many adverse risk predictors in the elderly has a major impact on the suitability of the coronary artery lesion for PCI and is inherent in their higher procedural risk. There is a high incidence of multivessel CAD in patients with lower EFs. One study noted that 50% of patients over the age of 75 versus 33% of younger patients have multivessel disease, with some 13% of those over age 80 having left main coronary disease (27). Thus, in the early balloon era, only 31% of patients in their 80s were considered suitable candidates for angioplasty because of diffuse extensive CAD (27,28). With the rise of improved PCI techniques such as stenting, interventions for many of these advanced “type C” lesions are now routine, but the modified American Heart Association (AHA)/American College of Cardiology (ACC) characteristics still predict poorer overall short- and long-term success in this setting (29).

As a consequence of more extensive disease, elderly patients are often more unstable upon presentation for intervention than younger patients, not uncommonly having had prior silent infarctions (30). They have a higher frequency of class III/IV angina, which is present during intervention in as many as 70% of patients over 65 and in an even higher number of those over age 80, compared with less than 50% of younger patients (6,14,23–26,31).

OUTCOMES OF BALLOON ANGIOPLASTY IN THE ELDERLY

Initial results in elderly patients undergoing angioplasty in the early 1980s showed relatively low acute success rates, higher procedural complications, and higher mortality (14,23). The results have been age-dependent, with those over age 75 having poorer outcomes than younger patients (14,23–26,32,33). Elderly patients who underwent...
angioplasty at the Mayo Clinic between 1980 and 1989 showed procedural mortality of 1.2% for patients below age 75 but 6.7% for those over age 75 (6). This is in keeping with other large centers during the same period (34). In a large Medicare database of some 20,000 patients, Jollis et al. reported in-hospital mortality rates of 7% in patients over age 80 with angioplasty (35). With lower profile balloons, perfusion balloons, in-lab monitoring of anticoagulation status, increasing operator experience, and occasional use of bailout stenting, angioplasty success had significantly improved by the early 1990s to an acceptable level of 88% to 93% (34,36) in elderly patients with single-vessel disease, but was still lower in the oldest subjects.

Compared with the 1980s, results of angioplasties performed at Mayo Clinic from 1990 to 1992 showed a 50% drop in hospital mortality to 0.8% in patients aged 65 to 74 years and to 3% in those over age 75 (36). The rate of complications had also fallen during this time period, with procedural infarction rates in those over age 65 falling to 2.2% (vs. 3.9%, previously) and emergency bypass rates of 0.65% (vs. 5.5%).

More recently, Feldman et al. (37) evaluated the effect of age on outcome in the New York State Registry using data from 2000/2001. In this series, 10,964 patients had undergone emergency PCI and 71,176 patients elective PCI. Patients were divided into three age groups, below 60 years, 60 to 80 years, and above 80 years. In both elective and emergency PCI, elderly patients had more comorbidities. Age was strongly predictive of in-hospital mortality for both elective and emergency cases. In the elective cases, mortality was 0.1%, 0.4%, and 1.1%, respectively ($p < 0.05$); in the emergency cases, mortality was 1.0%, 4.1%, and 11.5%, respectively ($p < 0.05$).

Other medical complications postprocedure have also been a particular concern in the elderly. After angioplasty, Maiello and colleagues (38) described a 1.1% rate of renal insufficiency and a 5.4% rate of need for transfusion in patients over 70. As a result, the elderly tend to have longer hospital stays, although this may be favorably altered by careful attention to the amount of contrast dye used, better preprocedural hydration, less aggressive anticoagulant dosing, and the use of smaller caliber catheters. Of interest, longer hospital stays are associated with higher mortality, presumably reflecting complications that necessitate an extended hospitalization.

**PREDICTORS OF POOR EARLY OUTCOME WITH ANGIOPLASTY IN THE ELDERLY**

The strongest predictor of hospital death in the elderly is the presence of extensive or multiple vessel coronary disease (39). Maiello and colleagues (40) showed a high success rate, approaching 100% in patients over the age of 75, in single vessel angioplasty versus a success rate in multiple vessel treatment of only 52%. The overall procedural success rate depends on the additive number of vessels treated. Calcified coronary artery lesions have definitely been predictors of failed angioplasty procedures in the past, and, even in contemporary practice with stenting, are associated with poorer long-term event-free survival (29,41), because of a higher subsequent need for repeat revascularization procedures.

**LONG-TERM OUTCOMES IN THE ELDERLY FOLLOWING ANGIOPLASTY**

The long-term results after a successful angioplasty in the elderly have shown consistent improvement over time. By the early 1990s, Buffet et al. (32) and Thompson et al. (6) had shown four-year survival of 83% and 86%, respectively. The overall long-term survival
rates were not significantly different among those over and those under 75 years of age. However, there was less satisfactory event-free survival in patients over 75 years in these series (6,32) that was probably less because of restenosis than to progression of their underlying advanced atherosclerotic disease. Restenosis rates have been quite similar, in the 31% to 44% range, with angioplasty in patients over 80 years, patients between 65 and 79, and in younger patients (24,42–45).

The strongest predictor of event-free survival in the elderly postangioplasty is the extent of CAD. DeJaegere et al. (46) reported an 81% event-free survival at four years postangioplasty in patients over age 70 with single-vessel disease versus 45% in patients with multivessel disease. The extent of disease was also a multivariate risk predictor in a prior review of the Mayo Clinic angioplasty experience in the elderly (39). Other predictors of long-term event-free survival were the left ventricular systolic function, the presence of unstable angina, and the number of noncardiac medical problems (35,36,39,43–47).

Clearly, there is a wide variation in risk in angioplasty patients, especially in the elderly. The number of adverse risk factors present greatly impacts the long-term risk of death or myocardial infarction. In a Mayo Clinic series with stratification by the number of risk predictors, we noted that elderly patients undergoing angioplasty with three-vessel CAD, recent CHF, and two other concomitant medical problems had three-year survival rates free of myocardial infarction of only 66%, while in the absence of these factors, survival was 96% (39).

ELDERLY PATIENTS WITH MULTIVESSEL DISEASE: ANGIOPLASTY VERSUS SURGERY

Some authors have suggested that the reduced event-free survival seen in the elderly may relate to the frequency of incomplete revascularization with angioplasty, but others believe, it indirectly reflects the greater extent of active coronary disease in this population (39,46,47) associated with more coronary risk factors. Nonetheless, the relative lack of complete and durable revascularization achieved with angioplasty for multivessel disease in the elderly is a prime reason why many elderly patients will ultimately require surgery (48).

This was one of the major findings in the elderly subset of the largest randomized multivessel coronary angioplasty versus bypass study in the Bypass Angioplasty Revascularization Investigation (BARI) trial, which enrolled 1829 patients from 1988 to 1991 (49). No significant difference in 30-day mortality (1.7% in each) was noted in the 709 patients aged 65 to 80 years compared with younger patients who were randomized, although many patients with angioplasty required repeat revascularization and some ultimately had CABG. In all age groups, only the subset with diabetes showed higher mortality with angioplasty versus bypass surgery, and this is definitely a consideration in elderly patients undergoing angioplasty in lieu of CABG (50). The rate of strokes with CABG was significantly higher in the elderly than with angioplasty (49). Since the prohibitively high revascularization rates with angioplasty seen in the overall population in BARI (52% vs. 6% with CABG at five years), stenting has become the preferred therapy. Importantly, even in the present era, not all lesions are suitable for stenting, and some may still be better treated with balloon angioplasty; hence these results are still clinically relevant in as many as 25% to 30% of PCI involving the elderly, particularly in small vessels, branch vessels, or those with heavy calcification.

The randomized Stent or Surgery (SOS) trial evaluated age-related outcomes in 988 patients treated with either CABG \((n = 500)\) or stent-assisted PCI \((n = 488)\) (51). The
impact of age on outcome was studied in patients aged 65 years or below versus older patients. In the older patients who were randomized to PCI, 19.5% required repeat revascularization versus 3.4% of patients treated with CABG \((p < 0.001)\). In the older patients, one-year health status was assessed, which included physical limitations, frequency of angina, and quality of life, and the outcome was similar irrespective of whether the initial treatment was PCI or CABG \((51)\).

**RESULTS OF CORONARY STENTING IN THE ELDERLY**

Coronary stenting has become the dominant revascularization mode in the elderly with one- and two-vessel disease and, occasionally, in those with three-vessel CAD felt to be too high risk for CABG. In the early stenting era, Yokoi et al. \((52)\) reported initial successful stent results to be lower in those over 75 years compared with younger patients for the initial Palmaz–Schatz stent \((86\% \text{ vs. } 95\%)\), with associated higher hospital mortality \((4.1\% \text{ vs. } 1.2\%)\). By the mid 1990s, the procedural success rate with lower profile, more easily deliverable stents had improved to 90.8% and 90.2% in two series by Chevalier et al. and Batchelor et al. \((53,54)\) of 142 and 7472 octogenarians, respectively, but with poorer results compared with younger patients’ success rates of 95.5%. Overall in-hospital mortality was still around 3.5%, and combined death/infarction and stroke risks were 5.2%; stenting was associated with better procedural success rates and lower need for repeat revascularization, but higher vascular complication rates \((52)\). Procedural success with stenting has increased compared with results from the early series and now ranges between 90\% and 97\% at major medical centers \((55–57)\).

A recent National Heart, Lung, and Blood Institutes Dynamic Registry study of PCIs from 1997 to 1999 \((58)\) compared 307 patients over 80 years of age (oldest), 1776 patients aged 65 to 79 years (older), and 2537 patients below 65 years (youngest). Successful procedural treatment of all lesions attempted was lower in those over versus those under age 80 \((84\% \text{ vs. } 92–93\%)\) despite similar IIb/IIIa platelet glycoprotein receptor inhibitor use \((26\% \text{ to } 29\%)\), similar stent rates \((72\% \text{ to } 73\%)\), and similar rates of rotational atherectomy \((5.2\% \text{ to } 7.2\%)\). Accounting for the lesser success in the oldest patients was a higher burden of coronary disease with more vessels (two or more in 15\% vs. 9.4\% vs. 9.4\%), more lesions (2 or more in 39.1\% vs. 34.2\% vs. 29.0\%), and more graft vessels \((8.5\% \text{ vs. } 8.3\% \text{ vs. } 3.9\%)\) treated compared with the two younger groups. Complication rates included higher stroke rates in those over age 80 \((1.0\% \text{ vs. } 0.5\% \text{ older vs. } 0.2\% \text{ younger})\), higher in-hospital mortality \((4.6\% \text{ vs. } 2.2\% \text{ vs. } 0.6\%)\) and more nonfatal myocardial infarctions \((6.2\% \text{ vs. } 3.1\% \text{ vs. } 2.2\%)\). One-year survival, although lower with increasing age, was identical to the age-expected mortality rates of the general population, suggesting that successful revascularization in the elderly is beneficial \((58)\).

**LONG-TERM RESULTS OF STENTING IN THE ELDERLY**

The earliest study that included a large number of elderly patients undergoing stenting with first-generation stents reported increased angiographic restenosis rates in 137 patients aged 75 years and older compared with 2551 younger individuals \((47\% \text{ vs. } 28\%)\) \((57)\). The presence of more advanced coronary disease in those over 75 years old versus those under 75 years old was evidenced by higher rates of stenting in multiple vessels \((44\% \text{ vs. } 27\%)\), left main \((7.35\% \text{ vs. } 1.5\%)\), ostial lesions \((15.5\% \text{ vs. } 7\%)\), and more frequent use of rotational atherectomy for debulking of calcified lesions in the elderly (notably, all factors in restenosis). Other studies by Chauhan et al. \((55)\) in
300 octogenarians, Abizaid et al. (56) in over 700 patients over age 70, and Alfonso et al. (59) in 378 patients over age 65 years have all shown similar clinical restenosis rates when compared with younger patients, but higher in-hospital mortality rates (1.3% to 3.0% in those over age 80 vs. 0.2% to 0.7% in younger patients), procedural infarction rates (7% to 10% vs. 2%), bleeding and vascular complications (5% vs. 1.0%), and subsequent one-year mortality (5% to 9% vs. 1% to 2%). Many studies with coronary interventions in the past have shown that late events are related mostly to repeat revascularization; despite similar restenosis rates, patients over 75 are less likely to undergo repeat revascularization, possibly because of less aggressive late treatment (60).

Drug-eluting stents have come to dominate interventional cardiology on the basis of the results of multiple randomized clinical trials that document marked reduction in both angiographic and clinical restenosis compared with conventional bare metal stents. There is limited information on the effect of age on outcome in this setting.

Vlaar et al. (61) analyzed 2453 patients undergoing drug-eluting stents at Mayo Clinic to evaluate the effect of age on outcomes. They classified patients into four different age groups: 50–59, 60–69, 70–79, and over 80 years old. Although procedural success was 97.5% in the latter group, this was still significantly less than in younger patients ($p = 0.044$). In-hospital mortality in patients aged over 80 years was 1.9% versus 0.9% in those patients 50 to 59 years. At 12 months of follow-up, target lesion revascularization rates were similar across the age groups at 4.8%, 5.6%, 4.3%, and 4.4% for the 50 to 59, 60 to 69, 70 to 79, and over 80 years age-groups, respectively. There were, however, significantly higher major adverse cardiac event rates at older ages, with rates of 7.5%, 8.9%, 11.0%, and 16.2%, respectively, for the four groups. Also, the mortality was higher in the octogenarians at 8.8% versus rates of 1.4%, 2.3%, and 4.7% in the three younger groups, respectively ($p \leq 0.001$). Despite this increase in overall mortality, the life expectancy of octogenarians undergoing drug-eluting stent treatment was similar to that of the general Minnesota population of the same age and gender (61).

Hassani et al. (62) also evaluated the outcome of drug-eluting stents in patients aged 80 years or above compared with younger patients. There were 339 octogenarians and 2827 younger patients. As could be expected, octogenarians had more adverse characteristics including more chronic renal failure, CHF, more extensive CAD, and lower EF. Multivariate analysis identified age over 80 years at the index procedure, cardiogenic shock, Q-wave myocardial infarction, and length of hospital stay to be independent predictors of mortality.

**PREDICTORS OF STENTING OUTCOME IN THE ELDERLY**

In a landmark study reflecting relatively current practice in PCI, Klein et al. (62) examined 8828 octogenarians undergoing intervention with predominant stenting (75%) in the 100,000 patient ACC-National Cardiovascular Data Registry from 1998 to 2000. The most important factor identified as a predictor of in-hospital death in the elderly was the presence of an acute myocardial infarction within six hours of PCI. For those over age 80, treated in a nonemergency fashion, the overall mortality was only 1.4% (vs. 13.8% for intervention in the setting of acute infarction), with low stroke rates (0.34%) and infrequent renal failure (1.5%), but with a notable degree of vascular complications (3.0%). The overall success rate was 93%, with slightly lower success in those with acute infarctions (91% vs. 94%). Other predictors of increased procedural mortality in octogenarians, if present (vs. if not present), included decreased EF, acute renal failure (29% vs. 3.2%), peripheral vascular disease with vascular complications (8.2% vs. 3.3%),
procedural Q-wave infarction (17.4% vs. 3.7%), and stroke (17% vs. 3.3%). Predictors of higher mortality were two to three times as frequent with acute myocardial infarction.

Other studies have identified the presence of multivessel disease, CHF, left main disease, thrombus, vein graft treatment, cardiogenic shock, chronic renal failure, prior myocardial infarction, prior CABG as additive predictors of poor outcome of PCI in the elderly in the stent era (7,8). Factors associated with adverse procedural outcome with PCI are listed in Table 1.

### PCI FOR ACUTE INFARCTION IN THE ELDERLY

The Global Utilization of Streptokinase and t-PA for Occluded Coronary Arteries-I (GUSTO-I) trial was one of the first to recognize the survival advantage of rapid restoration of normal levels of coronary blood flow in the infarct-related artery. Reperfusion therapy was introduced with thrombolytic agents, but it became apparent that in the elderly, particularly those over age 75, thrombolysis resulted in worrisome levels of disabling and/or fatal strokes, negating some of the survival benefits of opened coronary arteries (63,64).

The risk appeared to be higher with tissue plasminogen activator therapy than with streptokinase, leading to preferential use of the latter in the elderly. As angioplasty, and later stenting techniques, became accepted therapy in chronic stable angina, their use as primary therapy in acute infarction in the elderly was tested in a number of small studies. Initial success rates varied widely and ranged between 61 and 92%, depending on age and the presence/absence of multivessel disease, left ventricular dysfunction, bleeding complications, and other comorbidities.

### ACUTE CORONARY SYNDROMES IN THE ELDERLY

There has been great interest in acute coronary syndromes in the elderly. This relates to the frequent comorbidities in this group and the higher rates of adverse outcomes.

### ST-Elevation Myocardial Infarction

Reperfusion therapy has become the standard of care in ST-elevation myocardial infarction (STEMI). In the past 10 years, changes in the approach to reperfusion have
evolved substantially, driven in part by the increased incidence of fatal and/or disabling strokes after thrombolysis in the elderly, especially those older than 75 years. This has resulted in greater acceptance of an invasive approach.

Gottlieb et al. (66) studied trends in the management of acute infarction in 1475 patients aged 75 years or above in Israel. Over the 10 years during 1992–2002, there was a significant increase in reperfusion therapy (from 27% to 48%), medical therapy including aspirin (from 53% to 88%), β blockers (from 18% to 65%), and angiotensin-converting enzyme inhibitors (from 26% to 63%). During the same decade, there was a 42% reduction in the 30-day mortality (from 27% to 16%, OR 0.57, 95% CI 0.36–0.93) and a 20% reduction in one-year mortality (from 37% to 29%).

Marked regional differences in care have been documented in older patients. Ko et al. (67) compared procedural and medication use and 30-day risk standardized mortality in 38,886 American fee-for-service Medicare beneficiaries versus 5634 similarly aged Canadian patients and found significant differences. Overall, the use of invasive procedures was higher in the United States [38.5% vs. 16.8% (p < 0.001)]. Despite this, the standardized 30-day mortality was not different. This finding has not been universal. Harpaz et al. (68) studied 1009 patients aged 76 years and above in all coronary care units in Israel. Those patients who underwent coronary angiography were on average 2.2 years younger; in addition, they had a higher systolic pressure, lower Killip class, and lesser prevalence of STEMI. Of the patients who underwent coronary angiography, 67% underwent revascularization either with PCI or with surgery. These authors also found that in patients who underwent angiography, both the crude mortality as well as the adjusted one-year mortality rates were less (21% vs. 37% p < 0.0001).

There are several potential different reasons for the differences in outcome from PCI in the elderly with STEMI. Popitean et al. (69) evaluated the French regional survey data. They found that with increasing age, there are increased prehospital delays. In addition, once in hospital, the time to diagnosis has been found to be increased in elderly patients, in part because of atypical symptom presentations. The elderly also received less guideline-based medication regimens (70,71).

These and other data have moved the practice of reperfusion in STEMI toward an invasive strategy. Sakai et al. (72) evaluated 1087 patients treated by primary angioplasty and subdivided them by age 75 years and older and those younger than 75 years. They found that the mortality in the older patients was higher (8.1% vs. 4.0% p = 0.0057). Successful reperfusion was achieved in 91.6% and 92.9% of patients, respectively. When reperfusion was successful, cardiac mortality in older patients was not statistically significantly higher (4.6% vs. 2.8% p = 0.14). Guagliumi et al. (73) analyzed the outcome of elderly patients in the Controlled Abciximab and Device Investigation to Lower Late Angioplasty Complications (CADILLAC) trial of PCI. They found that one-year mortality increased for each decile of age. In those patients below 55 years, one-year mortality was 1.6% but increased to 11.1% for patients above 75 years (p < 0.0001). In addition, elderly patients had increased rates of stroke and major bleeding.

An early, randomized trial of reperfusion therapy for acute infarction specifically in the elderly was recently reported by de Boer et al. (74). This study of 87 patients over age 75 years randomized 46 patients to PCI versus 41 patients to streptokinase therapy. Of the 41 patients who actually received PCI (two had CABG, two received MED, one died preangiography), 90% had a successful result, with 51% receiving stents. The results were dramatic, with in-hospital mortality (7% vs. 20%), 30-day mortality rates (7% vs. 22%), 1-year mortality (13% vs. 41%), stroke risk (1% vs. 7%), and reinfarction rates (2% vs. 15%), all showing significant advantages of PCI over thrombolysis.
Non–ST-Elevation Myocardial Infarction

Elderly patients with non–ST-elevation myocardial infarction (NSTEMI) also have more adverse baseline clinical characteristics as is seen with patients with STEMI. They are also treated differently than younger patients. Yan et al. (75) stratified 4627 patients admitted with an acute coronary syndrome in the Canadian Acute Coronary Syndrome Registry into three groups (<65, 65–74, and ≥75 years of age). Across a broad spectrum, the elderly patients were at higher risk but were less likely to receive evidence-based medical therapy or to undergo revascularization. In another large survey in Europe, Rosengren et al. (76) analyzed 10,253 patients from 25 countries. There was a significant inverse association between age and the likelihood of presenting with a STEMI. As has been true in other studies, elderly patients were investigated less intensively and were more apt to be seen by a general medical physician rather than a cardiologist (76).

Substantial international variability in the care of elderly patients with acute coronary syndrome has also been documented. Alexander et al. (77) used data from the Sibrafiban versus Aspirin to Yield Maximum Protection from Ischemic Heart Events Post-Acute Coronary Syndromes (SYMPHONY) trials. They contrasted 1794 patients 75 years of age or above versus 14,043 below 75 years. Elderly patients, overall, were at higher risk at the time of the index presentation and underwent catheterization less frequently than younger patients. Absolute catheterization rates varied from 27% to 77%. Revascularization rates also varied. Of interest, in this study performance of cardiac catheterization was not an independent predictor of 90-day death or the combined endpoint of death or myocardial infarction.

Finally, Avezum et al. (78) evaluated age in the Global Registry of Acute Coronary Events (GRACE) registry of 24,165 acute coronary syndrome patients from 14 countries. The medical therapies of aspirin, β blockers, thrombolytic therapy, statins, and IIb/IIIa glycoprotein inhibitors were all used less frequently with increasing age. In addition, performance of coronary angiography and PCI was also less frequent in the older patients.

ACUTE INTERVENTION IN CARDIOGENIC SHOCK COMPPLICATING MYOCARDIAL INFARCTION IN THE ELDERLY

The Should We Emergently Revascularize Occluded Coronaries for Cardiogenic Shock (SHOCK) trial suggested a survival advantage with rapid revascularization for younger patients with cardiogenic shock (79). Unfortunately, there was a trend toward poorer outcome in those over age 75 who were revascularized versus those receiving aggressive medical treatment, which included use of an intra-aortic balloon pump (75% vs. 53% 30-day mortality). A portion of this trial occurred during an era of lower stent use as well as lesser use of IIb/IIIa receptor inhibitors.

More recent observational studies of acute intervention in the elderly for cardiogenic shock have suggested significant survival advantages with stenting. The large GRACE investigation of 583 patients (April 1999 to June 2001) shows overall mortality rates of 59%, with rates of only 35% in those treated with stenting (19). Two smaller studies have shown similar benefits, but have attributed much of the effect to synergy between use of stents and the use of the IIb/IIIa receptor inhibitor, abciximab. In 96 and 13 patients, respectively, Chan et al. (79) and Giri et al. (80) noted angiographic success rates (TIMI-3 flow) of 85% in the abciximab-stenting patients versus lower rates (64–67%) with stenting alone, angioplasty plus abciximab or angioplasty alone. Mortality in the abciximab-stenting groups was 13% to 22% (vs. 36–38% in both angioplasty groups and 36–52% mortality in the stent only groups), indicating significant benefit of stenting
Percutaneous Coronary Intervention in the Elderly

plus abcixamab in these high-risk patients. Prasad et al. (82) evaluated the outcome of elderly patients with shock at Mayo Clinic who underwent PCI. In 61 patients with a mean age of 79.5 years, in-hospital mortality occurred in 44%. However, the one-year survival after hospital discharge was 75%. Although the momentum is building toward a preferred role for acute interventions in elderly patients with acute cardiogenic shock, one must await randomized multicenter trials to make firm recommendations. In an elderly patient with minimal prior comorbidities, PCI with stenting in acute cardiogenic shock may be a consideration, whereas it may not be appropriate in a frail patient with numerous health concerns.

MULTIVESSEL STENTING RESULTS IN THE ELDERLY

With the advent of better stenting strategies, better techniques/devices to address higher risk ACC/AHA type C lesions, and the rise of antiplatelet therapies, outcomes with PCI have improved in general (83). Thus, PCI has become an attractive, if not preferred, alternative to bypass surgery, especially in candidates not favorable for or desiring CABG. The questions are whether it is appropriate to perform multivessel stenting in the elderly, and what are the benefits/problems in comparison to CABG?

A number of contemporary trials of multivessel stenting compared with CABG for extensive disease have been reported. The largest trial, Arterial Revascularization Therapy Study (ARTS), randomly assigned 1205 patients (600 to PCI vs. 605 to CABG) (84). The results in the nondiabetics showed low one-year mortality in both assigned therapies (1.6% PCI vs. 2.8% CABG), with an overall 76% event-free survival at 18 months with stents compared with 88% with CABG ($p < 0.0001$). Some 11.7% of PCI-assigned patients (vs. 2.9% CABG patients) required subsequent PCI while 3.9% later underwent CABG (vs. 0.6% CABG patients). Although CABG showed significantly better symptom-free survival, the stenting results were much more favorable than those at a similar follow-up stage in the BARI angioplasty subset (50), despite 70% of patients having complex type B2/C lesions. Results in the 208 randomized diabetic patients were not as attractive with PCI as with CABG (63% vs. 84% event-free survival at 18 months), possibly related to the low 3.5% rate of abciximab use in this high-risk subset.

In contrast, it was possibly the 28% use of abciximab and the higher procedural CABG mortality (5.7% vs. 0.9%) that allowed multivessel stenting to show a better 18-month survival rate than CABG (96.9% vs. 92.5%; $p < 0.02$) in the Argentine Randomized Study: Coronary Angioplasty with Stenting versus Coronary Bypass Surgery in patients with Multiple-Vessel Disease (ERACI)-2 trial of multivessel therapy options (85). In the 225-patient PCI arm versus a similar-sized CABG arm, there was also a lower long-term rate of infarction (2.3% vs. 6.6%; $p < 0.02$), but the rate of repeat revascularization with PCI versus CABG patients was 16.8% compared with 4.8%. The randomized SOS trial, with 500 CABG patients and 488 multivessel PCI patients, also showed a high rate of two-year repeat procedures of 21% in the PCI group versus 6% in the CABG patients (51). The low surgical mortality rate of 2% was in keeping with some 50% of patients having stable angina; the mortality rate in patients with unstable angina in the ERACI trial was 7.9%.

Perhaps one of the most relevant trials to date in the elderly and in high-risk patients was the recently reported Angina With Serious Operative Mortality Evaluation (AWESOME) trial. It enrolled 454 medically refractory veterans from 1995 to 2000 with one or more high-risk characteristics: age over 70 years, cardiac shock needing intraaortic balloon pumping, EF less than 35%, prior CABG, and recent infarction (86). With 222 patients receiving multivessel stenting and 232 receiving CABG—and at least 50%
over age 67—it showed comparably low 30-day (5% vs. 3%), six-month (10% vs. 6%), and three-year mortalities (21% vs. 20%) with CABG versus PCI, respectively. Thus, elderly patients, who are at high risk due to one or more of the above risk factors, may be able to avoid the longer recovery of CABG and live just as long with multivessel stenting.

OPTIONS FOR REVASCULARIZATION IN THE ELDERLY

From early revascularization era, a definite role for CABG has emerged in higher risk patient groups on the basis of its consistent beneficial effect on long-term survival and in reducing anginal symptoms (11,50,87–89). The success of CABG versus PCI in the elderly has been attributed mostly to CABG’s greater efficacy at achieving complete revascularization of all or most affected vessel territories in the setting of multivessel CAD, left main CAD, advanced AHA/ACC lesion class, and/or lower EF (9,43,51,82–91). Whereas balloon angioplasty in the 1980s and early 1990s was an accepted therapy for single-vessel disease (92,93), the frequent problem of restenosis, as demonstrated by five-year revascularization rates exceeding 50% in BARI, has limited its widespread application in multivessel diseases, particularly in the presence of diabetes (49,50).

CABG has been utilized as a viable revascularization option in older patients with extensive CAD because past studies with PCI, even those with stenting, have shown frequent recurrent angina leading to repeat PCIs and ultimate need for CABG in up to 20% of patients (49–51,54–56,84,86). Unfortunately, CABG surgery in the elderly is not entirely a benign procedure. The overall mortality rate of CABG in a 1990 Medicare database of nearly 24,500 patients over age 80 was higher compared with patients aged 65 to 70, with poorer in-hospital mortality (11.5% vs. 4.4%), one-year mortality (19.3% vs. 7.9%), and three-year mortality (28.8% vs. 13.1%) rates (94). Many elderly patients are also at substantial risk of perioperative myocardial infarction, pneumonia, renal failure, prolonged mechanical ventilation, and neurological events, with rates between 2 and 10% (49,95). Given these risks, in addition to cognitive impairments seen in approximately 60% short term and approximately 20% long-term post-CABG in the elderly (95–97), many patients will not regain their previous level of function and, thus, suffer a loss in their quality of life. Some elderly patients, particularly those who have extensive CAD, a recent or prior myocardial infarction, prior revascularization, or additional comorbidities, will have even higher potential morbidity and mortality with CABG.

The search for a viable alternative to CABG has continued to make steady progress. Recent PCI studies with predominant stent use demonstrate comparable or slightly better survival with PCI versus CABG but have still failed to avoid the subsequent need for additional revascularization in the PCI group, especially in the setting of diabetes (81–86). The question, when deciding upon the most suitable revascularization modality, is whether the higher procedural morbidity/mortality with CABG is justified by the 20% lower five-year need for repeat revascularization compared with PCI. In the setting of numerous comorbidities or frailty, elderly patients may be better served with moderate-duration symptomatic improvement offered by PCI. Indeed, one issue many studies fail to recognize when reporting poorer long-term survival in the elderly after either CABG or PCI is that the long-term survival with a successful revascularization modality is not very different compared with others of similar age (8,94). Factors favoring preferential attempts at PCI with stenting compared with those favoring CABG in the elderly are listed in Table 2.
The challenge in the near future will be to further define the role for PCI versus CABG, especially in the elderly and patients with extensive CAD and significant comorbidities. Drug-eluting stents, by promising a solution to the problem of restenosis, may well provide the opportunity for multivessel PCI to surpass CABG as the preferred revascularization therapy in general and in the elderly in particular.

### GOALS OF REVASCULARIZATION IN THE ELDERLY

One drawback of comparing results of angioplasty and PCI in the elderly versus younger patients is that the goals of the procedure may differ by age. More often, elderly patients are poor candidates for surgery, with the palliative goal of reducing symptoms, whereas younger patients are freer to consider the options: either the most effective procedure that will avoid the need for future procedures versus the one that will interfere the least with their active lifestyle. The options in the elderly are often less applicable or consist of picking the “better” of two “unappealing” therapeutic alternatives.

In summary, results employing PCI with stenting and careful use of IIb/IIIa inhibitors have advanced interventional methods to a degree where stenting may be the preferred revascularization option in the oldest and/or sickest patients. Hopefully, clinical trialists will continue to address revascularization issues in the elderly, recognizing their unique needs.

### Table 2  Factors Favoring Better Revascularization Results with Either Percutaneous Coronary Intervention or Coronary Artery Bypass Surgery in the Elderly

<table>
<thead>
<tr>
<th>Patient characteristics</th>
<th>Coronal bypass better</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age over 80</td>
<td>Diabetes (extensive disease)</td>
</tr>
<tr>
<td>Numerous comorbid illnesses</td>
<td>No major comorbid illnesses</td>
</tr>
<tr>
<td>Frail health/limited life expectancy</td>
<td>Active lifestyle/expect longevity</td>
</tr>
<tr>
<td>Major depression</td>
<td>Dedicated to lifestyle changes</td>
</tr>
<tr>
<td>Poor motivation to rehabilitate</td>
<td>Great motivation to rehabilitate</td>
</tr>
<tr>
<td>Morbid obesity/severe COPD</td>
<td>Thin, athletic in past</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Angiographic characteristics</th>
<th>Coronal bypass better</th>
</tr>
</thead>
<tbody>
<tr>
<td>Focal/limited 1- or 2-vessel CAD</td>
<td>3-vessel CAD/left main CAD</td>
</tr>
<tr>
<td>Good left ventricular function</td>
<td>Poor left ventricular function</td>
</tr>
<tr>
<td>AHA/ACC type A, B1 lesion</td>
<td>AHA/ACC type B2, C lesion</td>
</tr>
<tr>
<td>Bifurcation: risk to small branch</td>
<td>Bifurcation: risk to large branch</td>
</tr>
<tr>
<td>Crossable total occlusion</td>
<td>Uncrossable occlusion/large area of “jeopardized” tissue</td>
</tr>
<tr>
<td>Acute MI/cardiogenic shock</td>
<td>Stable CAD</td>
</tr>
<tr>
<td>Procedure goal: symptom relief</td>
<td>Goal: survival/symptom relief</td>
</tr>
</tbody>
</table>

Abbreviations: COPD, Chronic obstructive pulmonary disease; CAD, coronary artery disease; AHA/ACC, American Heart Association/American College of Cardiology; MI, myocardial infarction.
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Exercise Training and Cardiac Rehabilitation in Older Cardiac Patients

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The goals of cardiac rehabilitation in older coronary populations are to decrease cardiac disability, cardiac-related symptoms, and to extend disability-free survival. Compared with younger patients with coronary heart disease (CHD), older patients have higher rates of disability and mobility limitations, and a diminished exercise capacity (1–3). Coronary artery disease (CAD) in the elderly is also characterized by a greater severity of angiographic disease (4), more severe and more diffuse left ventricular systolic dysfunction (5), and increased levels of peripheral vascular and left ventricular stiffness also termed “diastolic dysfunction,” compared with younger cardiac patients (6). The higher rate of diastolic dysfunction results in the fact that dyspnea is a more common symptom than chest pain in many older patients suffering a myocardial infarction (7,8). Compared with older men, older women with CHD have a higher prevalence of chronic heart failure, a greater prevalence of coronary risk factors, a more complex clinical course, and higher rates of physical disability (1,9). Despite the fact that primary prevention has resulted in a lower prevalence of CAD in the elderly, the rapidly increasing size of the older population is such that the absolute number of older patients with CHD is increasing (10,11). Cardiac rehabilitation exercise training designed to decrease disability and overall coronary risk in older CHD patients should come to play an increasingly important role as the size of the older CHD population continues to grow.

CARDIAC DISABILITY

The Social Security Administration has no guidelines or definitions for cardiac disability for patients over the age of 65 years, because at this age disability pensions are simply converted to “old-age” pensions (12). In practice, disability in older CHD patients is defined by limitations in physical activity, mobility, and ability to perform activities of daily living with an underlying psychological component. Data from the Framingham Disability Study provides insight into the effects of various CHD manifestations on disability and mobility in older populations (1). The Framingham Disability Study included 2576 participants and yielded a quantitative assessment of levels of physical and
social disability in older adults, based upon self-reported information. The measures of disability were primarily based upon three questions: “Are you able to walk up and down stairs to the second floor without help?” “Are you able to walk a half mile without help?” and “Are you able to do heavy work around the house, like shoveling snow or washing windows, walls, or floors without help?” The presence of any negative responses determined a component of physical disability.

At a given age, women were more likely to report disability than men, and the presence of CHD was a major predictor of activity limitations in both men and women (Table 1). In the 55- to 69-year age group, 49% of men and 67% of women with CHD were disabled as compared with 9% of men and 25% of women without CHD. In coronary patients over the age of 70 years with symptoms of angina pectoris or chronic heart failure, disability was reported by over 80% of women and 55% of men. The presence of CHD in the “older-old” was particularly powerful, with estimated disability rates of up to 76% in men 75 years of age and older.

Other studies on this topic are complementary to the Framingham study. In the Medical Outcomes Study, angina was related to the total physical activity score in older patients, although past myocardial infarction was not (13). Chirikos and Nickel studied 976 men and women hospitalized for acute coronary syndromes (myocardial infarction or unstable angina). By multivariate analysis, they found that the presence of cardiac disease, in particular angina pectoris, was predictive of disability at 6, 18, and 24 months of follow-up (14). In a subsequent analysis, they found that angina was more disabling in older women than older men, supporting the findings of the Framingham study (2).

Data from our laboratory provides further insight into the determinants of physical functional capacity in older coronary patients (15). A group of 51 men and women over the age of 65 years with established chronic CHD underwent comprehensive evaluations with exercise echocardiography, measurement of peak aerobic capacity, strength, and body composition along with detailed clinical histories, and self-reported measures of physical function and mental depression. Univariate predictors of physical function score included peak aerobic capacity, depression score, handgrip strength, gender, and comorbidity score (16). By multivariate analysis, the only independent predictors of physical function score were peak aerobic capacity and depression score. Left ventricular

### Table 1 Framingham Disability Study by Age and Coronary Disease Status

<table>
<thead>
<tr>
<th></th>
<th>Percentage with disability (age 55–69 yr)</th>
<th>Percentage with disability (age 70–88 yr)</th>
</tr>
</thead>
<tbody>
<tr>
<td>No CAD or CHF</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Women</td>
<td>25</td>
<td>49</td>
</tr>
<tr>
<td>Men</td>
<td>9</td>
<td>27</td>
</tr>
<tr>
<td>Coronary heart disease</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Women</td>
<td>67</td>
<td>79</td>
</tr>
<tr>
<td>Men</td>
<td>49</td>
<td>49</td>
</tr>
<tr>
<td>Angina pectoris</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Women</td>
<td>67</td>
<td>84</td>
</tr>
<tr>
<td>Men</td>
<td>57</td>
<td>56</td>
</tr>
<tr>
<td>Chronic heart failure</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Women</td>
<td>80</td>
<td>88</td>
</tr>
<tr>
<td>Men</td>
<td>43</td>
<td>57</td>
</tr>
</tbody>
</table>

*Abbreviations:* CHF, chronic heart failure; CAD, coronary artery disease.

*Source:* From Ref. 1.
systolic function, which varies inversely with infarct size, was not related to the physical function score (15).

In summary, the presence of clinical CHD is a powerful predictor of disability and mobility limitations in the elderly. Disability rates are highest in women, the older-old, and in the presence of angina pectoris, chronic heart failure, and mental depression.

AEROBIC TRAINING

The goals of cardiac rehabilitation exercise training in older coronary populations are, above all, to decrease cardiac disability and to extend disability-free survival. These goals are accomplished by programs that will increase aerobic capacity, muscle strength, and flexibility and which will provide associated psychosocial and cardiac risk factor benefits. Exercise training programs in the elderly also need to take into account commonly associated comorbidities that can alter the modalities and intensities of the exercise stimulus that is required. These include, but are not limited to, chronic heart failure, arthritis, chronic lung disease, diabetes, osteoporosis, and peripheral and cerebrovascular disease. In middle-aged coronary patients and in patients with chronic heart failure, reduced cardiovascular fitness [peak oxygen uptake (VO2)] is a primary clinical predictor of impaired physical function and of clinical survival (17,18). Furthermore, favorable training-induced changes in peak aerobic capacity are associated with a lower mortality for patients with the greatest training effect (19). Meta-analyses of randomized trials of cardiac rehabilitation, including over 4000 patients, document a 25% decreased mortality over an average follow-up of three years after cardiac rehabilitation (20,21). These studies are limited, however, by the inclusion of few patients over the age of 65, and the fact that over 80% of the subjects were male. Most of these studies antedated current thrombolytic and interventional approaches to acute myocardial infarction as well as the many interventions available for secondary prevention, such as lipid lowering, antiplatelet therapy, β-adrenergic blockade, and angiotensin-converting–enzyme inhibitors. The Cochrane Database systematic review of cardiac rehabilitation in 2001 extends these findings to contemporary populations, although these remain primarily middle-aged patients (22).

In older coronary patients, there are no definitive randomized clinical trial data assessing whether exercise conditioning prolongs life. Therefore, the goals of rehabilitation in the elderly need to focus on improving physical functioning and extending disability-free survival. It should be noted, however, that a large observational study, the British Regional Heart Study of almost 6000 men with established CHD, found that regular light-to-moderate physical activity was associated with a lower five-year all-cause mortality (23). Secondarily, exercise rehabilitation plays an important role in coordination of coronary risk factor therapy, including management of hypertension, lipid abnormalities, insulin resistance, and obesity (24).

The cardiac rehabilitation literature supports the safety and efficacy of exercise training regimens in older coronary patients (3,25–28). Compared with younger coronary patients, older patients are significantly less fit at entry into a rehabilitation program one to three months after suffering a major coronary event, such as myocardial infarction or coronary bypass surgery (3,29) (Fig. 1). In a cross-sectional analysis of cardiac patients, peak aerobic capacity decreased by 40% in men and 33% in women from age 40 to age 80 (29). Also notable is that older patients after coronary artery bypass grafting surgery are significantly less fit compared with patients after myocardial infarction or a percutaneous coronary intervention (29). However, after three months of aerobic conditioning, older
coronary patients derive a similar relative training benefit as younger patients, with peak VO\textsubscript{2} increasing 16% to 20%, effectively distancing themselves from mobility limitations and disability (Fig. 2). Training programs have been extended to a year and longer with long-term maintenance of exercise-related benefits (27,30).

The effects of aerobic exercise training programs on submaximal exercise response in older coronary patients are more relevant to the performance of daily activities than the maximal exercise response. In a study of 45 older coronary patients, mean age 69 ± 6 years, subjected to a three-month aerobic conditioning program, submaximal indices of exercise

\begin{figure}[h]
\centering
\includegraphics[width=\textwidth]{figure1.png}
\caption{Peak aerobic capacity (peak VO\textsubscript{2}) by age and gender entering cardiac rehabilitation. Upper graph (hatched lines) are women. Lower graph (solid lines) are men. \textit{Abbreviation:} VO\textsubscript{2}, oxygen uptake. \textit{Source:} From Ref. 29.}
\end{figure}

\begin{figure}[h]
\centering
\includegraphics[width=\textwidth]{figure2.png}
\caption{Peak aerobic capacity (Peak VO\textsubscript{2}) before and after conditioning in older and younger patient groups. *\(p < 0.001\) compared with preconditioning. \textit{Abbreviation:} VO\textsubscript{2}, oxygen uptake. \textit{Source:} From Ref. 3.}
\end{figure}
performance were closely studied (31). Training effects were assessed during an exhaustive submaximal exercise protocol, with patients exercising at a steady intensity of 80% of a previously measured peak aerobic capacity. Outcome measures included endurance time, serum lactate, perceived exertion, heart rate, blood pressure, and expired ventilatory measures. Exhaustive endurance time increased by more than 40% after conditioning, with associated decreases in serum lactate, perceived exertion, minute ventilation, heart rate, and systolic blood pressure during relatively steady state exercise. Respiratory exchange ratio during steady state exercise, an indicator of substrate utilization, decreased, indicating a shift toward greater use of free fatty acids as a more efficient metabolic fuel. Activities that were exhaustive before training became sustainable for extended periods of time at a lower perceived exertion.

The mechanisms of physiological adaptations to aerobic exercise conditioning in the elderly may differ somewhat from those seen in younger (i.e., middle-aged) coronary patients. In younger patients, physiological responses to training include both peripheral adaptations (skeletal muscle and vascular), which result in a widened arteriovenous oxygen difference at maximal exercise (32,33), and cardiac adaptations, which include increases in cardiac dimensions, stroke work, cardiac output, and afterload-corrected indices of left ventricular function (34–37). In older coronary patients, coronary and peripheral vascular diseases are superimposed on “age-related” increases in left ventricular and arterial wall thickness and stiffness (6,8,39), which may reduce their adaptability to remodeling. We found that, after three months of intensive aerobic conditioning in 60 older coronary patients (mean age 68 ± 5 years, range 62–82 years), conditioning-induced adaptations were localized almost exclusively to the periphery (40). Peak exercise cardiac output, hyperemic calf blood flow, and vascular conductance were unaffected by the conditioning program. In contrast, at 3 and 12 months, arteriovenous oxygen difference at peak exercise was increased in intervention subjects but not in age-matched controls, which explains the 16% increase in peak aerobic capacity. Histological analysis of skeletal muscle documented a 34% increase in capillary density and a 23% increase in oxidative enzyme capacity after three months. After 12 months, an increase in individual fiber area was seen compared with baseline measures. Thus, even after 12 months of aerobic exercise, in contrast with middle-aged coronary patients, we saw no discernible improvements in cardiac output or calf blood flow. It is acknowledged, however, that the absolute amount of exercise performed by older coronary patients is less than that performed by younger patients, and this may potentially confound comparisons of physiological response to training by age group.

Practical issues related to the implementation of exercise training programs in older coronary patients include the frequent need for training regimens to be adjusted to accommodate the presence of comorbidities such as arthritis, diabetes, and peripheral vascular disease (Table 2). The least fit individuals are often unable to sustain exercise for

**Table 2** Implementing Exercise in Older Coronary Patients

- Optimally performed in the cardiac rehabilitation setting
- Intensity of exercise generally based on an exercise tolerance test
- In severely disabled patients, forego exercise test and begin with low level interval training on treadmill and/or cycle
- Resistance training based on single-repetition maximal testing
- Advance intensity actively
- Long-term goals and follow-up
extended periods and do well with repeated intermittent brief bouts of exercise (often termed “interval training”) that are gradually extended. Some authors recommend longer-term exercise programs for the elderly, partly related to their low baseline functional capacity (30). It should however, be noted, that even patients who use canes and walkers can perform an exercise test and can train on a treadmill with surround bars or on a cycle ergometer.

Despite the documented value of exercise regimens in older patients and the low baseline measures of functional capacity, older coronary patients are far less likely than younger patients to participate in cardiac rehabilitation (41). Our data documented a 21% participation rate in cardiac rehabilitation for patients over the age of 62 years who recently suffered a coronary event and who lived within 1 hour driving time of the rehabilitation center, compared with a 4% participation rate in younger patients (41). By far, the most powerful predictor of cardiac rehabilitation participation in the clinical setting was the strength of the primary physician’s recommendation for participation as described by the patient. The physician’s recommendation was scored from 1 to 5, ranging from no encouragement to participate (a score of 1) to a strong encouragement to participate (a score of 5). When the recommendation was weak (a score of 1–3), a 2% participation rate was noted, compared with a rate of 66% when it was strong (a score of 4–5). Older women had a lower participation rate than men (15% vs. 25%; p = 0.06); this difference was primarily related to lower physician recommendation scores for women than men (42). Other factors weighing against participation for women include more comorbid conditions, greater difficulty with transportation, lower likelihood of being married, and higher likelihood of having a dependent spouse at home.

RESISTANCE TRAINING

Resistance training has been advocated as a particularly useful intervention in older coronary patients for several reasons (43–45). First and foremost, even “normal” aging is associated with a significant loss of muscle mass and strength, related both to diminished activity profiles and to decreased rates of muscle protein synthesis (43,46–48). Furthermore, in older populations ranging from healthy community living elders to institutionalized octogenarians, resistance training has been demonstrated to improve walking endurance, muscle mass, and strength (49,50). In coronary patients, aging-related musculoskeletal abnormalities are superimposed upon activity restrictions related to chronic disease (51), and diminished muscle mass and strength, termed “sarcopenia,” is even more severe.

In a study that focused upon resistance training in older CAD patients who had recently suffered a myocardial infarction, relative increases in strength were found to be similar to increases seen in younger CAD patients (44). In older women with chronic CHD, where the negative effects of age, gender, and chronic disease all conspire to result in a severe loss of strength and function (15), the effects of strength training have recently been studied (52). Brochu et al. assessed the effects of six months of resistance training on strength, endurance, and on a physical performance test designed to assess physical function during practical household activities in 30 older women, mean age 71 ± 5 years (53). Compared with patients randomized to a control group, strength-trained women increased strength, endurance, and capacity to perform a wide range of household activities such as carrying groceries, doing household activities, and climbing stairs. The increase in strength after resistance training correlated with improvements in the overall physical function score (Fig. 3).
From a practical point of view, the onset of upper body resistance training should be delayed until three months after coronary bypass surgery to allow for full sternal healing, while it can commence as soon as one month postmyocardial infarction after performance of a satisfactory baseline exercise tolerance test. The resistance training program should include training of the leg extensor muscles to assist with walking, stair climbing and fall prevention, and upper body training to aid in the lifting and pushing required for the performance of daily household activities. Training is based upon the performance of a single-repetition maximal (1-RM) lift supplemented by a Borg scale for perceived exertion (54). Patients begin their resistance training with 8 to 10 repetitions of each exercise at 40% to 50% of their 1-RM for a given exercise and gradually increase exercise intensity, as tolerated, to 50% to 80% of updated 1-RMs.

SCREENING AND IMPLEMENTATION

Optimally, older coronary patients begin exercise training only after a careful screening process, which should include an electrocardiographically monitored exercise tolerance test, strength measures, and a clinical review, including an analysis of disease severity and questionnaire or interview-derived data regarding physical and psychosocial function. Diagnostic categories appropriate for consideration of cardiac rehabilitation exercise training in older cardiac patients include myocardial infarction, stable angina pectoris, coronary bypass surgery, percutaneous coronary revascularization (angioplasty, or stenting), heart valve replacement, and chronic heart failure.

Exercise modalities should include options for aerobic, resistance, and flexibility exercise. Aerobic choices include treadmills, a walking course, cycles, airdynes, and rowers. Aerobic exercise is often guided by an exercise heart rate range and/or scales of perceived exertion such as the Borg scale. A gradual increment of exercise heart rate from...
60% to 65% of maximal attained heart rate to higher levels of up to 85% is balanced against the greater risk of injury at higher levels and past demonstration of measurable benefits even with low levels of exercise (55). It has been observed that older coronary patients are less likely to exercise to a physiological maximum at their baseline exercise test than younger patients; therefore, strict adherence to an exercise heart rate range is often inappropriate (3). Duration of the exercise stimulus can begin with very brief, intermittent bouts of exercise, gradually increasing to 20 to 25 minutes or longer. Special considerations in the elderly include that training regimens often need to be adjusted to accommodate the presence of comorbidities. For example, patients with hip or knee arthritis may do better with cycling or rowing exercises to avoid the weight bearing of treadmill walking. However, walking is generally a preferred modality because of its direct relevance to daily activities. Finally, it should be noted that, for many elders, flexibility, or lack thereof, can be an exercise-limiting factor. Flexibility exercises can be as simple as 5 to 10 minutes of stretching per day to more complex protocols of yoga and tai chi.

Gender Issues

Healthy older women have lower levels of habitual physical activity and physical functioning than older men, explained, in part, by lower strength and muscle mass (56–58). Older women with CAD further curtail their activities because of apprehension regarding the safety of specific physical activities, which compounds their deconditioning. Following a coronary event, women have lower fitness levels than men (29), yet are less likely to be referred to an exercise-based rehabilitation program by their physicians (41). This distinction may relate, in part, to the older age of women after infarction, compared with men, or to higher rates of angina pectoris, but is most likely related to the physician misunderstanding regarding the benefits of rehabilitation in the most severely debilitated patients. Women make similar improvements in aerobic fitness and in muscular strength compared with men in rehabilitation programs (43,44). The current model of cardiac rehabilitation was developed primarily in middle-aged male coronary patients in the 1960s and 1970s. The differing clinical profile of women in cardiac rehabilitation may require a different model relevant to their older age, increased prevalence of comorbid conditions, more prominent cardiac risk factor profiles, higher rates of depression, higher risk of recurrent coronary events, and differing personal preferences (59–62).

Supervised Vs. Home Exercise

Roughly, only 15% of eligible patients in the United States receive cardiac rehabilitation services, with the lowest participation rates noted in older patients (24,41). In many cases, cardiac rehabilitation programs are not geographically available (63), whereas in other cases, patients are unable to travel, or the primary physician does not recommended formal rehabilitation. While cardiac rehabilitation services have classically been delivered on-site at an established exercise training facility, a need to expand preventive cardiology services to include the majority of eligible patients in a cost-effective manner necessitates a redefinition of this classical model.

The development of alternate approaches to the delivery of cardiac rehabilitation services is an ongoing process, with a goal of expanding the base of patients who receive services at the lowest possible healthcare costs. Older patients tend to require a more “hands-on” approach early in the rehabilitative process, but often can transition to
a home program with appropriate follow-up. Case management, that is, evaluation and management of the exercise program and risk factors for the individual patient by a nurse “case manager” allows for the individualization of preventive care in health-care delivery systems that focus on efficiency and outcomes. Exercise programs can be individualized, with moderate- and high-risk patients referred to a rehabilitation program for closer supervision and monitoring.

CARDIAC REHABILITATION ON CORONARY RISK FACTORS

Exercise plays an important adjunctive role in the management of blood lipid levels, obesity, blood pressure, and psychological factors such as social isolation and mental depression. In older coronary populations, exercise rehabilitation has well-defined metabolic benefits that include improved blood lipid values, decreased body fat, improved glucose tolerance, and lower blood pressure (28,64,65). In addition, cardiac rehabilitation in the elderly has been shown to have important effects on mental health, which include decreased measures of depression, anxiety, and hostility (Table 3) (66–69). These measures, in summary, constitute important outcome measures for older CHD patients engaging in therapeutic exercise.

Cardiac rehabilitation programs have been termed “secondary prevention centers” and thus should function as a location to systematically measure and treat coronary risk factors with both lifestyle approaches (exercise and nutrition) and pharmacological therapy. For example, a systematic approach to measuring lipid profiles in all patients entering cardiac rehabilitation, with an active stance towards pharmacological therapy, resulted in a tripling of the number of patients that attain nationally recognized therapeutic lipid goals (70). Similarly, blood-pressure monitoring and treatment, and obesity assessment and treatment should be coordinated in the cardiac rehabilitation setting (71).

The magnitude of exercise-related effects on blood lipid measures depends, in part, on whether or not there is associated weight loss. In a study of cardiac rehabilitation without weight loss, lipid effects were relatively modest with high density lipoprotein (HDL)-cholesterol increasing by 8%, but no significant effects on low density lipoprotein (LDL)-cholesterol, triglyceride levels, or glucose levels (64). On the other hand, when exercise was associated with 10 lbs of exercise-induced weight loss, favorable effects were noted on serum triglycerides (−24%), HDL-cholesterol (+7%), on the atherogenic ratio [total cholesterol/HDL-cholesterol (−14%)], and fasting serum insulin levels (−22%) (72). Exercise rehabilitation has also been shown to be associated with a decrease in the high-sensitive C-reactive protein, a predictor of prognosis after myocardial infarction.

Table 3 Noncardiac Benefits of Exercise Rehabilitation in Older Coronary Patients

<table>
<thead>
<tr>
<th>Effect</th>
<th>Ref.</th>
</tr>
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<tbody>
<tr>
<td>Increased HDL cholesterol (+8–10%)</td>
<td>28,64</td>
</tr>
<tr>
<td>Decreased triglycerides (−10–25%)</td>
<td></td>
</tr>
<tr>
<td>Decreased body fat (−1–2%)</td>
<td>28,64</td>
</tr>
<tr>
<td>Improved glucose tolerance</td>
<td>65</td>
</tr>
<tr>
<td>Lowered blood pressure (−5–7 mmHg systolic)</td>
<td>66</td>
</tr>
<tr>
<td>Diminished depression, anxiety, and hostility</td>
<td>28,67–69</td>
</tr>
</tbody>
</table>

Abbreviation: HDL, high-density lipoprotein.
(73). The benefits in older coronary patients of lipid-lowering, smoking-cessation, angiotensin-converting–enzyme inhibition, antiplatelet agents, and β-adrenergic blockade have all been demonstrated in appropriately selected populations (74,75).

FUTURE DIRECTIONS

As the older cardiac population continues to grow in size and complexity, the role of cardiac rehabilitation in the elderly should proportionately expand. The effects of aerobic and resistance-training protocols on measures of physical functioning need to be better studied in older coronary populations, with the inclusion of patients disabled by angina or chronic heart failure. Whether training regimens can improve physical functioning in the most severely disabled patients is of particular importance, although preventing disability in the less severely affected “younger-old” is also a priority. Effects of exercise regimens on other important outcomes, including lipid levels, blood pressure measures, insulin levels, body composition, and body fat distribution need to be further studied to better define expected benefits of rehabilitation. Finally, whether training regimens can affect the economics of health care is crucial, especially if costly hospitalizations and/or home-care services can be minimized.

In summary, the older coronary population is a highly disabled group, yet quite heterogeneous as to physical functioning and disease severity. Cardiac rehabilitation training programs have been demonstrated to be safe and to improve aerobic fitness capacity, muscular strength, and cardiac risk factors. Exercise training may, in fact, reverse and prevent cardiac disability. Thus, cardiac rehabilitation can pay great medical, social, and economic dividends in the older coronary population.

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Exercise Training and Cardiac Rehabilitation in Older Cardiac Patients

Aortic Valve Disease in the Elderly

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AORTIC STENOSIS

Etiology and Prevalence

Valvular aortic stenosis (AS) in elderly patients is usually due to stiffening, scarring, and calcification of the aortic valve leaflets. The commissures are not fused as in rheumatic AS. Calcific deposits in the aortic valve are common in elderly patients and may lead to valvular AS (1–7). Aortic cuspal calcium was present in 295 of 752 men (36%), mean age 80 years, and in 672 of 1663 women (40%), mean age 82 years (6). Of 2358 patients, mean age 81 years, 378 (16%) had valvular AS, 981 (42%) had valvular aortic sclerosis (thickening of or calcific deposits on the aortic valve cusps with a peak flow velocity across the aortic valve $\leq 1.5$ m/sec), and 999 (42%) had no valvular AS or aortic sclerosis (7). Calcific deposits in the aortic valve were present in 22 of 40 necropsy patients (55%) aged 90 to 103 years (2). Calcium of the aortic valve and mitral annulus may coexist (1–3,8,9).

In the Helsinki Aging study, calcification of the aortic valve was diagnosed by Doppler echocardiography in 28% of 76 patients aged 55 to 71 years, in 48% of 197 patients aged 75 to 76 years, in 55% of 155 patients aged 80 to 81 years, and in 75% of 124 patients aged 85 to 86 years (5). Aortic valve calcification, aortic sclerosis, and mitral annular calcium (MAC) are degenerative processes (1,2,10–12) accounting for their high prevalence in an elderly population.

Otto et al. (11) demonstrated that the early lesion of degenerative AS is an active inflammatory process with some similarities to atherosclerosis, including lipid deposition, macrophage and T-cell infiltration, and basement membrane disruption. In a prospective study of 571 unselected patients, mean age 82 years, 292 patients (51%) had calcified or thickened aortic cusps or root (13). A total serum cholesterol greater than or equal
to 200 mg/dL, a history of hypertension, diabetes mellitus, and a serum high-density lipoprotein cholesterol less than 35 mg/dL were more prevalent in elderly patients with calcified or thickened aortic cusps or root than in elderly patients with normal aortic cusps and root (13).

In the Helsinki Aging Study, age, hypertension, and a low body mass index were independent predictors of aortic valve calcification (14). In 5201 patients older than 65 years of age in the Cardiovascular Health Study, independent clinical factors associated with degenerative aortic valve disease included age, male gender, smoking, history of hypertension, height, and high lipoprotein (a) and low-density lipoprotein cholesterol levels (12). In 1275 elderly patients, mean age 81 years, AS was present in 52 of 202 patients (26%) with 40% to 100% extracranial carotid arterial disease (ECAD) and in 162 of 1073 patients (15%) with 0% to 39% ECAD (15). In 2987 elderly patients, mean age 81 years, symptomatic peripheral arterial disease was present in 193 of 462 patients (42%) with AS and in 639 of 2525 patients (25%) without AS (16).

In 290 patients, mean age 79 years, with valvular AS who had follow-up Doppler echocardiograms, elderly patients with MAC had a greater reduction in aortic valve area/year than those without MAC (17). Cigarette smoking and hypercholesterolemia were significant independent risk factors for the progression of valvular AS in 102 patients, mean age 76 years, who had follow-up Doppler echocardiograms (18). Palta et al. (19) also found that cigarette smoking and hypercholesterolemia accelerate the progression of AS. These and other data suggest that aortic valve calcium, MAC, and coronary atherosclerosis in elderly patients have similar predisposing factors (11–21).

A retrospective analysis of 180 elderly patients with mild AS who had follow-up Doppler echocardiograms at or after two years showed that significant independent predictors of the progression of AS were male gender, cigarette smoking, hypertension, diabetes mellitus, a serum low-density lipoprotein cholesterol greater than or equal to 125 mg/dL at follow-up, a serum high-density lipoprotein cholesterol less than 35 mg/dL at follow-up, and use of statins (inverse association) (22). Novaro et al. (23) reported in a retrospective analysis of 174 patients, mean age 68 years, with mild to moderate AS that statin therapy reduced the progression of AS.

In a retrospective study of 156 patients, mean age 77 years, with AS, at 3.7-year follow-up, statin therapy reduced the progression of AS by 54% (24). There is need for data from a long-term, large, prospective, randomized controlled trial of intensive statin therapy in patients with AS, especially in patients with mild AS.

The frequency of AS increases with age. Valvular AS diagnosed by Doppler echocardiography was present in 141 of 924 men (15%), mean age 80 years, and in 322 of 1881 women (17%), mean age 81 years (25). Severe valvular AS (peak gradient across aortic valve of $\geq 50$ mmHg or aortic valve area $< 0.75$ cm$^2$) was diagnosed in 62 of 2805 elderly patients (2%) (25). Moderate valvular AS (peak gradient across aortic valve of 26–49 mmHg or aortic valve area of 0.75–1.49 cm$^2$) was present in 149 of 2805 elderly patients (5%) (25). Mild valvular AS (peak gradient across aortic valve of 10–25 mmHg or aortic valve area $\geq 1.50$ cm$^2$) occurred in 25 of 2805 elderly patients (9%) (25). In 924 elderly men, mean age 80 years, AS was present in 36 of 236 African-Americans (15%), in 19 of 135 Hispanics (14%), and in 86 of 553 whites (16%) (25). In 1881 elderly women, mean age 81 years, AS was present in 84 of 494 African-Americans (17%), in 33 of 188 Hispanics (18%), and in 205 of 1199 white women (17%) (25). In 501 unselected patients aged 75 to 86 years in the Helsinki Aging Study, critical AS was present in 3% and moderate to severe AS in 5% of the 501 elderly patients (5).
Pathophysiology

In valvular AS, there is resistance to ejection of blood from the left ventricle (LV) into the aorta, with a pressure gradient across the aortic valve during systole and an increase in LV systolic pressure. The pressure overload on the LV leads to concentric LV hypertrophy, with an increase in LV wall thickness and mass, normalizing systolic wall stress, and maintenance of normal LV ejection fraction and cardiac output (26,27). A compensated hyperdynamic response is common in elderly women (28). Elderly patients with a comparable degree of AS have more impairment of LV diastolic function than do younger patients (29). Coronary vasodilator reserve is more severely impaired in the subendocardium in patients with LV hypertrophy caused by severe AS (30).

The compensatory concentric LV hypertrophy leads to abnormal LV compliance, LV diastolic dysfunction with reduced LV diastolic filling, and increased LV end-diastolic pressure, further increased by left atrial systole. It also develops left atrial enlargement. Atrial systole plays an important role in diastolic filling of the LV in patients with AS (31). Loss of effective atrial contraction may cause immediate clinical deterioration in patients with severe AS.

Sustained LV hypertrophy eventually leads to LV chamber dilatation with decreased LV ejection fraction and, ultimately, congestive heart failure (CHF). The stroke volume and cardiac output decrease, the mean left atrial and pulmonary capillary pressures increase, and pulmonary hypertension occurs. Elderly patients with both obstructive and non-obstructive coronary artery disease (CAD) have an increased incidence of LV enlargement and LV systolic dysfunction (32). In a percentage of elderly patients with AS, the LV ejection fraction will remain normal and LV diastolic dysfunction will be the main problem.

In 48 elderly patients with CHF associated with unoperated severe valvular AS, the LV ejection fraction was normal in 30 patients (63%) (33). The prognosis of patients with AS and LV diastolic dysfunction is usually better than that of patients with AS and LV systolic dysfunction, but is worse than that of patients without LV diastolic dysfunction (33,34).

Symptoms

Angina pectoris, syncope or near syncope, and CHF are the three classic manifestations of severe AS. Angina pectoris is the most common symptom associated with AS in elderly patients. Coexistent CAD is frequently present in these patients. However, angina pectoris may occur in the absence of CAD as a result of an increase in myocardial oxygen demand with a reduction in myocardial oxygen supply at the subendocardial level. Myocardial ischemia in patients with severe AS and normal coronary arteries is due to inadequate LV hypertrophy with increased LV systolic and diastolic wall stresses causing decreased coronary flow reserve (35).

Syncope in patients with AS may be caused by reduced cerebral perfusion following exertion when arterial pressure drops because of systemic vasodilatation in the presence of a fixed cardiac output. LV failure with a decrease in cardiac output may also cause syncope. In addition, syncope at rest may be caused by a marked reduction in cardiac output secondary to transient ventricular fibrillation or transient atrial fibrillation (AF) or transient atrioventricular block related to extension of the valve calcification into the conduction system. Coexistent cerebrovascular disease with transient cerebral ischemia may contribute to syncope in elderly patients with AS.

Exertional dyspnea, paroxysmal nocturnal dyspnea, orthopnea, and pulmonary edema may be caused by pulmonary venous hypertension associated with AS. Coexistent
CAD and hypertension may contribute to CHF in elderly patients with AS. AF may also precipitate CHF in these patients.

CHF, syncope, or angina pectoris was present in 36 of 40 elderly patients (90%) with severe AS, in 66 of 96 elderly patients (69%) with moderate valvular AS, and in 45 of 165 elderly patients (27%) with mild valvular AS (36).

Sudden death occurs mainly in symptomatic valvular AS patients (33,36–39). It may also occur in 3–5% of asymptomatic patients with AS (37,39). Marked fatigue and peripheral cyanosis in patients with AS may be caused by a low cardiac output. Cerebral emboli causing stroke or transient cerebral ischemic attack, bacterial endocarditis, and gastrointestinal bleeding may also occur in elderly patients with AS.

Signs

A systolic ejection murmur heard in the second right intercostal space, down the left sternal border toward or at the apex is classified as an aortic systolic ejection murmur (ASEM) (3,4,40,41). An ASEM is commonly heard in elderly patients (1,3,40), occurring in 265 of 565 unselected elderly patients (47%) (3). Of 220 elderly patients with an ASEM and technically adequate M-mode and two-dimensional echocardiograms of the aortic valve, 207 (94%) had aortic cuspal or root calcification or thickening (3). Of 75 elderly patients with an ASEM, valvular AS was diagnosed by continuous-wave Doppler echocardiography in 42 patients (56%) (41).

Table 1 shows that an ASEM was heard in 100% of 19 elderly patients with severe AS, 100% of 49 elderly patients with moderate AS, and 95% of 74 elderly patients with mild AS (4). However, the ASEM may become softer or absent in patients with CHF associated with severe AS because of a low cardiac output. The intensity and maximal location of the ASEM and transmission of the ASEM to the right carotid artery do not differentiate among mild, moderate, and severe AS (3,4,41). The ASEM may be heard only at the apex in some elderly patients with AS. The apical systolic ejection murmur may also be louder and more musical than the basal systolic ejection murmur in some elderly patients with AS. The intensity of the ASEM in valvular AS increases with squatting and by inhalation of amyl nitrite and decreases during the Valsalva maneuver.

Prolonged duration and late peaking of the ASEM best differentiate severe AS from mild AS (3,4,41). However, the physical signs do not distinguish between severe and moderate AS (Table 1) (4,41).

Table 1 Correlation of Physical Signs of Valvular Aortic Stenosis with the Severity of Aortic Stenosis in Elderly Patients

<table>
<thead>
<tr>
<th>Physical sign</th>
<th>Mild (n = 74) (%)</th>
<th>Moderate (n = 49) (%)</th>
<th>Severe (n = 19) (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>ASEM</td>
<td>95</td>
<td>100</td>
<td>100</td>
</tr>
<tr>
<td>Prolonged duration ASEM</td>
<td>3</td>
<td>63</td>
<td>84</td>
</tr>
<tr>
<td>Late-peaking ASEM</td>
<td>3</td>
<td>63</td>
<td>84</td>
</tr>
<tr>
<td>Prolonged carotid upstroke time</td>
<td>3</td>
<td>33</td>
<td>53</td>
</tr>
<tr>
<td>A2 absent</td>
<td>0</td>
<td>10</td>
<td>16</td>
</tr>
<tr>
<td>A2 decreased or absent</td>
<td>5</td>
<td>49</td>
<td>74</td>
</tr>
</tbody>
</table>

Abbreviations: AS, aortic stenosis; ASEM, aortic systolic ejection murmur; A2, aortic component of second heart sound.

Source: Adapted from Ref. 4.
A prolonged carotid upstroke time does not differentiate between severe and moderate AS in elderly patients (4). A prolonged carotid upstroke time was palpable in 3% of elderly patients with mild AS, in 33% of elderly patients with moderate AS, and in 53% of elderly patients with severe AS (Table 1) (4). Stiff noncompliant arteries may mask a prolonged carotid upstroke time in elderly patients with severe AS. The pulse pressure may also be normal or wide rather than narrow in elderly patients with severe AS because of loss of vascular elasticity. An aortic ejection click is rare in elderly patients with severe AS because of loss of vascular elasticity. An aortic ejection click is rare in elderly patients with AS because the valve cusps are immobile (4,41).

An absent or decreased A2 occurs more frequently in elderly patients with severe or moderate AS than in patients with mild AS (Table 1) (4,41). However, an absent or decreased A2 does not differentiate between severe and moderate AS (4,41). The presence of AF, reversed splitting of S2, or an audible fourth heart sound at the apex also does not differentiate between severe and moderate AS in elderly patients (41). The presence of a third heart sound in elderly patients with AS usually indicates the presence of LV systolic dysfunction and elevated LV filling pressure (42).

**Electrocardiography and Chest Roentgenography**

Table 2 shows that echocardiography is more sensitive than electrocardiography in detecting LV hypertrophy in elderly person with AS (4). Rounding of the LV border and apex may occur as a result of concentric LV hypertrophy. Poststenotic dilatation of the ascending aorta is commonly seen. Calcification of the aortic valve is best seen by echocardiography or fluoroscopy.

Involvement of the conduction system by calcific deposits may occur in elderly patients with AS. In a study of 51 elderly patients with AS who underwent aortic valve replacement, conduction defects occurred in 58% of 31 patients with MAC and in 25% of 20 patients without MAC (9). In another study of 77 elderly patients with AS, first-degree atrioventricular block occurred in 18% of patients, left bundle branch block in 10% of patients, intraventricular conduction defect in 6% of patients, right bundle branch block in 4% of patients, and left axis deviation in 17% of patients (43).

Complex ventricular arrhythmias may be detected by 24-hour ambulatory electrocardiograms in patients with AS. Elderly patients with complex ventricular arrhythmias associated with AS have a higher incidence of new coronary events than elderly patients with AS and no complex ventricular arrhythmias (44).

**Table 2** Prevalence of Electrocardiographic and Echocardiographic LVH in Elderly Patients with Mild, Moderate, and Severe Valvular AS

<table>
<thead>
<tr>
<th>Severity of Valvular AS</th>
<th>Mild (n = 74) (%)</th>
<th>Moderate (n = 49) (%)</th>
<th>Severe (n = 19) (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Electrocardiographic LVH</td>
<td>11</td>
<td>31</td>
<td>58</td>
</tr>
<tr>
<td>Echocardiographic LVH</td>
<td>74</td>
<td>96</td>
<td>100</td>
</tr>
</tbody>
</table>

*Abbreviations*: AS, aortic stenosis; LVH, left ventricular hypertrophy.

*Source*: Adapted from Ref. 4.
Echocardiography and Doppler Echocardiography

M-mode and two-dimensional echocardiography and Doppler echocardiography are very useful in the diagnosis of AS. Of 83 patients with CHF or angina pectoris and a systolic precordial murmur in whom severe AS was diagnosed by Doppler echocardiography, AS was not clinically diagnosed in 28 patients (34%) (45). Echocardiography can detect thickening, calcification, and reduced excursion of aortic valve leaflets (3). LV hypertrophy is best diagnosed by echocardiography (4). Chamber dimensions and measurements of LV end-systolic and end-diastolic volumes, LV ejection fraction, and assessment of global and regional LV wall motion give important information on LV systolic function.

Doppler echocardiography is used to measure peak and mean transvalvular gradients across the aortic valve and to identify associated valve lesions. Aortic valve area can be calculated by the continuity equation using pulsed Doppler echocardiography to measure LV outflow tract velocity, continuous-wave Doppler echocardiography to measure transvalvular flow velocity, and two-dimensional long-axis view to measure LV outflow tract area (46,47). Aortic valve area can be detected reliably by the continuity equation in elderly patients with AS (47). Figures 1 through 5 illustrate two-dimensional echocardiographic findings (Figs. 1 and 3), continuous-wave Doppler echocardiographic findings (Figs. 2 and 4), and simultaneous LV and femoral arterial pressure tracings (Fig. 5) in elderly patients with severe valvular AS.

Shah and Graham (48) reported that the agreement in quantitation of the severity of AS between Doppler echocardiography and cardiac catheterization was greater than 95%.

**Figure 1** Two-dimensional echocardiographic image from a parasternal long-axis view of a 93-year-old female with aortic stenosis and moderately depressed left ventricular function showing a fibrotic aortic valve and mitral annular calcification. *Abbreviations:* PS-LAX, parasternal long-axis view; RV, right ventricular cavity; LV, left ventricular cavity; IVS, interventricular septum; PW, posterior wall; CA ANUL, mitral annulus calcification; LA, left atrium; AO, aorta.
Aortic Valve Disease in the Elderly

**Figure 2** Continuous-wave Doppler recording of the velocity profile across the aortic valve in the same patient shown in Figure 1. A 52 mmHg gradient across the aortic valve is measured using the Bernoulli equation. Indexed aortic valve area measured by the continuity equation using Doppler data = 0.5 cm²/m².

**Figure 3** Two-dimensional echocardiographic image obtained in the same patient in Figures 1 and 2 from a short-axis parasternal view in which the aortic valve orifice is mapped, yielding an indexed area of 0.4 cm²/m².
Figure 4 Continuous-wave Doppler recording of the velocity profile across the aortic valve in an elderly patient with aortic stenosis and normal left ventricular systolic function. The indexed aortic valve area is 0.5 cm²/m² by both Gorlin’s formula and the Doppler continuity equation. The peak gradient across the aortic valve by Bernoulli’s equation is 81 mmHg, a value higher than that recorded in Figure 2 for the same indexed aortic valve area.

Abbreviations: Fem. Art., femoral artery pressure tracing; LV, left ventricular pressure tracing.

Figure 5 Simultaneous left ventricular and femoral artery pressure recordings obtained in the same patient in Figure 4 confirming a large gradient across the aortic valve with a maximum value of 81 mmHg (instantaneous pressure). Abbreviations: Fem. Art., femoral artery pressure tracing; LV, left ventricular pressure tracing.
Patients with a peak jet velocity greater than or equal to 4.5 m/sec had critical AS, and those with a peak jet velocity less than 3 m/sec had noncritical AS. Slater et al. (49) demonstrated a concordance between Doppler echocardiography and cardiac catheterization in the decision to operate or not to operate in 61 of 73 patients (84%) with valvular AS. In 75 patients, mean age 76 years, with valvular AS, the Bland–Altman plot showed that four of the 75 patients (5%) had disagreement between cardiac catheterization and Doppler echocardiography that was outside the 95% confidence limits (50).

Cardiac catheterization was performed in 105 patients in which Doppler echocardiography demonstrated an aortic valve area less than or equal to 0.75 cm² or a peak jet velocity greater than or equal to 4.5 m/sec, consistent with critical AS (51). Doppler echocardiography was 97% accurate in this subgroup. In this study, cardiac catheterization was performed in 133 patients with noncritical AS. Doppler echocardiography was 95% accurate in this subgroup. Although most elderly patients do not require cardiac catheterization before aortic valve surgery, they require selective coronary arteriography before aortic valve surgery. Patients in whom Doppler echocardiography shows a peak jet velocity between 3.6 and 4.4 m/sec and an aortic valve area greater than 0.8 cm² should undergo cardiac catheterization if they have cardiac symptoms attributable to AS (47). Patients with a peak jet velocity between 3 and 3.5 m/sec and a LV ejection fraction less than 50% may have severe AS, requiring aortic valve replacement, and should undergo cardiac catheterization (48). Patients with a peak jet velocity between 3 and 3.5 m/sec and a LV ejection fraction greater than 50% probably do not need aortic valve replacement (AVR) but should undergo cardiac catheterization if they have symptoms of severe AS (48).

### Natural History

Ross and Braunwald (37) found that the average survival rate was three years after the onset of angina pectoris in patients with severe AS. Ross and Braunwald (37) reported that the average survival rate after the onset of syncope in patients with severe AS was three years. Ross and Braunwald (37) demonstrated that the average survival rate after the onset of CHF in patients with severe AS was 1.5 to 2 years.

Patients with symptomatic severe valvular AS have a poor prognosis (36–39,52). At the National Institutes of Health, 52% of patients with symptomatic severe valvular AS not operated on were dead at five years (38,39). At 10-year follow-up, 90% of these patients were dead.

At four-year follow-up of patients aged 75 to 86 years in the Helsinki Aging Study, the incidence of cardiovascular mortality was 62% in patients with severe AS and 35% in patients with moderate AS (53). At four-year follow-up the incidence of total mortality was 76% in patients with severe AS and 50% in patients with moderate AS (53).

In a prospective study, at 19-month follow-up (range, 2–36 months), 90% of 30 patients with CHF associated with unoperated severe AS and a normal LV ejection fraction were dead (33). At 13-month follow-up (range, 2–24 months), 100% of 18 patients with CHF associated with unoperated severe AS and an abnormal LV ejection fraction were dead (33).

Table 3 shows the incidence of new coronary events in elderly patients with no, mild, moderate, and severe AS. Independent risk factors for new coronary events in this study were prior myocardial infarction, AS, male gender, and increasing age (36). In this prospective study, at 20-month follow-up of 40 elderly patients with severe AS, CHF, syncope, or angina pectoris was present in 36 of 37 patients (97%) who developed new coronary events and in none of 3 patients (0%) without new coronary events (36). At 32-month follow-up...
of 96 elderly patients with moderate valvular AS, CHF, syncope, or angina pectoris was present in 65 of 77 patients (84%) who developed new coronary events and in 1 of 19 patients (5%) without new coronary events (36). At 52-month follow-up of 165 elderly patients with mild AS, CHF, syncope, or angina pectoris was present in 40 of 103 patients (39%) who developed new coronary events and in 5 of 62 patients (8%) without new coronary events (36).

In a prospective study of 981 patients, mean age 82 years, with aortic sclerosis and of 999 patients, mean age 80 years, without valvular aortic sclerosis, elderly patients with aortic sclerosis had, at 46-month follow-up, a 1.8 times higher chance of developing a new coronary event than those without valvular aortic sclerosis (7). Otto et al. (54) also reported in 5621 men and women aged 65 years or above that AS and aortic sclerosis increased cardiovascular morbidity and mortality.

Kennedy et al. (55) followed 66 patients with moderate AS diagnosed by cardiac catheterization (aortic valve area 0.7–1.2 cm²). In 38 patients with symptomatic moderate AS and 28 patients with minimally symptomatic moderate AS, the probabilities of avoiding death from AS were 0.86 for patients and 1.0 for patients with minimally symptomatic moderate AS at one-year follow-up, 0.77 for patients with symptomatic AS and 1.0 for patients with minimally symptomatic AS at two years, 0.77 for patients with symptomatic AS and 0.96 for patients with minimally symptomatic AS at three years, and 0.70 for patients with symptomatic AS and 0.90 for patients with minimally symptomatic AS at four years (55). During 35-month mean follow-up in this study, 21 patients underwent aortic valve replacement.

Hammermeister et al. (56) followed 106 patients with unoperated AS in the Veterans Administration Cooperative Study on Valvular Heart Disease for five years. During follow-up, 60 of 106 patients (57%) died. Multivariate analysis demonstrated that measures of the severity of the AS, the presence of CAD, and the presence of CHF were the important predictors of survival in unoperated patients.

Studies have demonstrated that patients with asymptomatic severe AS are at low risk for death and can be followed until symptoms develop (57–60). Turina et al. (57) followed 17 patients with asymptomatic or mildly symptomatic AS. During the first two years, none died or had aortic valve surgery. At five-year follow-up, 94% were alive and 75% were free of cardiac events. Kelly et al. (58) followed 51 asymptomatic patients with severe AS. During 17-month follow-up, 21 (41%) of the patients became symptomatic. Only 2 of the 51 patients (4%) died of cardiac causes. In both patients, death was preceded by the development of angina pectoris or CHF. Pellikka et al. (59) observed that 113 of 143 patients (79%), mean age 72 years, with asymptomatic severe AS were not initially referred for AVR or percutaneous aortic balloon valvuloplasty. During 20-month follow-up, 37 of 113 patients (33%) became symptomatic. The actuarial probability of remaining free of cardiac events associated with AS, including cardiac death and aortic valve surgery,

**Table 3** Incidence of New Coronary Events in Older Persons with No, Mild, Moderate, and Severe Valvular AS

<table>
<thead>
<tr>
<th></th>
<th>No AS (n = 1496)</th>
<th>Mild AS (n = 165)</th>
<th>Moderate AS (n = 96)</th>
<th>Severe AS (n = 40)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (yr)</td>
<td>81</td>
<td>84</td>
<td>85</td>
<td>85</td>
</tr>
<tr>
<td>Follow-up (mo)</td>
<td>49</td>
<td>52</td>
<td>32</td>
<td>20</td>
</tr>
<tr>
<td>New coronary events</td>
<td>41%</td>
<td>62%</td>
<td>80%</td>
<td>93%</td>
</tr>
</tbody>
</table>

*Abbreviation:* AS, aortic stenosis.

*Source:* Adapted from Ref. 36.
Aortic Valve Disease in the Elderly

was 95% at six months, 93% at one year, and 74% at two years. No asymptomatic person with severe AS developed sudden death while remaining asymptomatic.

Rosenheck et al. (60) followed 126 patients with asymptomatic severe AS for 22 months. Eight patients died and 59 patients developed symptoms necessitating aortic valve replacement. Event-free survival was 67% at one year, 56% at two years, and 33% at four years. Five of the six deaths from cardiac disease were preceded by symptoms. Of the patients with moderately or severely calcified aortic valves whose aortic jet velocity increased by 0.3 m/sec or more within one year, 79% underwent AVR or died within two years.

When patients with low gradient AS due to abnormal LV ejection fraction are considered for aortic valve replacement, failure to respond to dobutamine and large preoperative LV end-systolic and end-diastolic volumes are poor prognostic signs (61–63). The American College of Cardiology/American Heart Association (ACC/AHA) guidelines state that dobutamine stress echocardiography is reasonable to evaluate patients with low-flow/low-gradient AS and abnormal LV ejection fraction (64).

Medical Management

Prophylactic antibiotics are not recommended to prevent bacterial endocarditis in patients with AS regardless of severity, according to AHA guidelines (65). Patients with CHF, exertional syncope, or angina pectoris associated with moderate or severe AS should undergo AVR promptly. Valvular surgery is the only definitive therapy in these elderly patients (64,66). Medical therapy does not relieve the mechanical obstruction to left ventricular outflow and does not relieve symptoms or progression of the disorder. Patients with asymptomatic AS should report the development of symptoms possibly related to AS immediately to the physician. If significant AS is present in asymptomatic elderly patients, clinical examination and an electrocardiogram and Doppler echocardiogram should be performed at six-month intervals. Nitrates should be used with caution in patients with angina pectoris and AS to prevent the occurrence of orthostatic hypotension and syncope. Diuretics should be used with caution in patients with CHF to prevent a decrease in cardiac output and hypotension. Vasodilators should be avoided. Digitalis should not be used in patients with CHF and a normal LV ejection fraction unless needed to control a rapid ventricular rate associated with AF.

Aortic Valve Replacement

Table 4 lists four class I indications and one class IIa indication for performing AVR in elderly patients with AS (64). AVR is the procedure of choice for symptomatic elderly patients with severe AS. Other class I indications for AVR in elderly patients with severe AS include patients undergoing coronary artery bypass graft (CABG), undergoing surgery

Table 4  ACC/AHA Class I Indications for Aortic Valve Replacement in Persons with Severe AS

| 1. Patients with symptomatic severe AS |
| 2. Patients with severe AS undergoing coronary artery bypass surgery |
| 3. Patients with severe AS undergoing surgery on the aorta or other heart valves |
| 4. Patients with severe AS and a left ventricular ejection fraction <50% |
| 5. Patients with moderate AS undergoing coronary artery bypass surgery or surgery on the aorta or other heart valves (class IIa indication) |

Abbreviations: ACC/AHA, American College of Cardiology/American Heart Association; AS, aortic stenosis

Source: Modified from Ref. 64.
on the aorta or other heart valves, and patients with a LV ejection fraction less than 50% (64). Patients with moderate AS undergoing CABG or surgery on the aorta or other heart valves have a class IIa indication for AVR (64).

Although the ACC/AHA guidelines do not recommend AVR in patients with asymptomatic severe AS and normal LV ejection fraction, there are some data suggesting otherwise. (67). Pai et al. (67) found in their database that 99 of 338 patients (29%), mean age 71 years, with asymptomatic severe AS had AVR during 3.5-year follow-up. Survival at one, two, and five years was 67%, 56%, and 38%, respectively, for nonoperated patients and 94%, 93%, and 90%, respectively, for those who had AVR (67). Echocardiography is recommended in asymptomatic patients with AS every one year for severe AS, every one to two years for moderate AS, and every three to five years for mild AS (64).

The bioprosthesis has less structural failure in elderly patients than in younger patients and may be preferable to the mechanical prosthetic valve for AS replacement in the elderly because of the anticoagulation issue (68,69). Patients with mechanical prostheses need anticoagulant therapy indefinitely. Patients with porcine bioprostheses may be treated with aspirin in a dose of 75 to 100 mg daily unless the patient has AF, abnormal LV ejection fraction, previous thromboembolism, or a hypercoagulable condition (64,70). Table 5 lists four class I indications and two class IIa indications for antithrombotic therapy in patients with AVR (64).

Arom et al. (71) performed AVR in 273 patients aged 70 to 89 years (mean age, 75 years), 162 with AVR alone, and 111 with AVR plus CABG. Operative mortality was 5%. Late mortality at 33-month follow-up was 18%. Actuarial analysis showed at five-year follow-up that overall survival was 66% for patients with AVR alone, 76% for patients with AVR plus CABG, and 74% for a similar age group in the general population.

A U.K. heart valve registry observed in 1100 patients aged 80 years or above (56% women) who underwent AVR that the 30-day mortality was 6.6% (72). The actuarial survival was 89% at one year, 79% at three years, 69% at five years, and 46% at eight

### Table 5  Class I Indications for Antithrombotic Therapy in Patients with AVR

1. After AVR with bileaflet mechanical or Medtronic Hall prostheses, in patients with no risk factors, administer warfarin to maintain INR between 2.0 and 3.0; if risk factors are present, the INR should be maintained between 2.5 and 3.5.
2. After AVR with Starr-Edwards valves or mechanical disc valves (other than Medtronic Hall prostheses), in patients with no risk factors, warfarin should be administered to maintain INR between 2.5 and 3.5.
3. After AVR with a bioprosthesis and no risk factors, administer aspirin in a dose of 75–100 mg daily.
4. After AVR with a bioprosthesis and risk factors, administer warfarin to maintain an INR between 2.0 and 3.0.
5. During the first 3 months after AVR with a mechanical prostheses, it is reasonable to give warfarin to maintain an INR between 2.5 and 3.5 (class IIa indication).
6. During the first 3 months after AVR with a bioprosthesis in patients with no risk factors, it is reasonable to give warfarin to maintain an INR between 2.0 and 3.0 (class IIa indication).

Risk factors include atrial fibrillation, prior thromboembolism, left ventricular systolic dysfunction, and hypercoagulable condition.

*Abbreviations: AVR, aortic valve replacement; INR, international normalized ratio.*

*Source: Modified from Ref. 64.*
Aortic Valve Disease in the Elderly

years. The survival of patients with severe AS, a LV ejection fraction less than 35%, and a low transvalvular gradient at one year and at four years was 82% and 78%, respectively, in 39 patients, mean age 73 years, who underwent AVR versus 41% and 15%, respectively, in 56 patients, mean age 75 years, in a control group (73). In 242 patients, mean age 83 years, with AS who had AVR, actuarial survival was 92% at one year and 66% at five years (74). Concomitant CABG did not affect late survival (74).

Paroxysmal or chronic AF is a risk factor for mortality in patients with severe AS and a LV ejection fraction less than or equal to 35% undergoing AVR (75). Of 83 patients, mean age 70 years, with severe AS and a LV ejection fraction less than or equal to 35%. Among them, 29 (35%) had paroxysmal or chronic AF (75). The perioperative mortality was 24% in the AF group versus 5.5% in the non-AF group \( (p = 0.03) \) (75).

AVR is associated with a reduction in LV mass and in improvement of LV diastolic filling (76–78). Hoffman and Burckhardt (79) performed a prospective study in 100 patients who had AVR. At 41-month follow-up, the yearly cardiac mortality rate was 8% in patients with electrocardiographic LV hypertrophy and repetitive ventricular premature complexes two or more couplets per 24 hours during 24-hour ambulatory monitoring and 0.6% in patients without either of these findings (79).

If LV systolic dysfunction in patients with severe AS is associated with critical narrowing of the aortic valve rather than myocardial fibrosis, it often improves after successful AVR (80). In 154 patients, mean age 73 years, with AS and a LV ejection fraction less than or equal to 35% who underwent AVR, the 30-day mortality was 9%. The five-year survival was 69% in patients without significant CAD and 39% in patients with significant CAD. New York Heart Association functional class III or IV was present in 58% of patients before surgery versus 7% of patients after surgery. Postoperative LV ejection fraction was measured in 76% of survivors at a mean of 14 months after surgery. Improvement in LV ejection fraction was found in 76% of patients (80).

Balloon Aortic Valvuloplasty

AVR is the procedure of choice for symptomatic elderly patients with severe AS. In a Mayo Clinic study, the actuarial survival of 50 elderly patients, mean age 77 years, with symptomatic severe AS in whom AVR was refused (45 patients) or deferred (5 patients) was 57% at one year, 37% at two years, and 25% at three years (81). Because of the poor survival in this group of patients, balloon aortic valvuloplasty should be considered when operative intervention is refused or deferred. On the basis of the available data, balloon aortic valvuloplasty should be considered for elderly patients with symptomatic severe AS who are not candidates for aortic valve surgery and possibly for patients with severe LV dysfunction as a bridge to subsequent valve surgery (82–84).

Percutaneous Transcatheter Implantation of Aortic Valve Prostheses

Percutaneous heart valve implantation may be performed in non-surgical patients with end-stage calcific AS (85,86). Ongoing trials will define the clinical role for this therapy.

Eighteen high-risk patients, mean age 76 years, with severe AS and moderate CAD amenable to percutaneous coronary intervention (PCI) had combined PCI followed by minimally invasive AVR (87). One of 18 patients (6%) died postoperatively with no late mortality after a mean follow-up of 19 months (97). This hybrid strategy may be a new therapeutic approach for elderly high-risk patients with combined CAD and severe AS.
AORTIC REGURGITATION

Etiology and Prevalence

Acute aortic regurgitation (AR) in elderly patients may be due to infective endocarditis, rheumatic fever, aortic dissection, trauma following prosthetic valve surgery, or rupture of the sinus of Valsalva, and causes sudden severe LV failure. Chronic AR in elderly patients may be caused by valve leaflet disease (secondary to any cause of AS, infective endocarditis, rheumatic fever, congenital heart disease, rheumatoid arthritis, ankylosing spondylitis, following prosthetic valve surgery, or myxomatous degeneration of the valve) or by aortic root disease. Examples of aortic root disease causing chronic AR in elderly patients include association with systemic hypertension, syphilitic aortitis, cystic medial necrosis of the aorta, ankylosing spondylitis, rheumatoid arthritis, Reiter’s disease, systemic lupus erythematosus, Ehler-Danlos syndrome, and pseudoxanthoma elasticum. Mild or moderate AR was also diagnosed by Doppler echocardiography in 9 of 29 patients (31%) with hypertrophic cardiomyopathy (88). Margonato et al. (89) linked the increased prevalence of AR with age to aortic valve thickening.

The prevalence of AR increases with age (89–91). In a prospective study of 450 unselected patients, mean age 82 years, AR was diagnosed by pulsed Doppler echocardiography in 39 of 114 men (34%) and in 92 of 336 women (27%) (91). Severe or moderate AR was diagnosed in 74 of 450 elderly patients (16%). Mild AR was diagnosed in 57 of 450 elderly patients (13%). In a prospective study of 924 men, mean age 80 years, and 1881 women, mean age 82 years, valvular AR was diagnosed by pulsed Doppler recordings of the aortic valve in 282 of 924 men (31%) and in 542 of 1881 women (29%) (25).

Pathophysiology

The primary determinants of AR volume are the regurgitant orifice area, the transvalvular pressure gradient, and the duration of diastole (92). Chronic AR increases LV ventricular end-diastolic volume. The largest LV end-diastolic volumes are seen in patients with chronic severe AR. LV stroke volume increases to maintain the forward stroke volume. The increased preload causes an increase in LV diastolic stress and the addition of sarcomeres in series. This results in an increase in the ratio of the LV chamber size to wall thickness. This pattern of LV hypertrophy is called eccentric LV hypertrophy.

Primary myocardial abnormalities or ischemia due to coexistent CAD depress the contractile state. LV diastolic compliance decreases, LV end-systolic volume increases, LV end-diastolic pressure rises, left atrial pressure increases, and pulmonary venous hypertension results. When the LV end-diastolic radius-to-wall thickness ratio rises, LV systolic wall stress increases abnormally because of the preload and afterload mismatch (27,93). Additional stress then decreases the LV ejection fraction response to exercise (94). Eventually, the LV ejection fraction, forward stroke volume, and effective cardiac output are decreased at rest. We demonstrated that an abnormal resting LV ejection fraction occurred in 8 of 25 elderly patients (32%) with CHF associated with chronic severe AR (95).

In patients with acute severe AR, the LV cannot adapt to the increased volume overload. Forward stroke volume falls, LV end-diastolic pressure increases rapidly to high levels, (96) and pulmonary hypertension and pulmonary edema result. The rapid rise of the LV end-diastolic pressure to exceed the left atrial pressure in early diastole causes premature closure of the mitral valve (97). This prevents backward transmission of the elevated LV end-diastolic pressure to the pulmonary venous bed.
Symptoms

Patients with acute AR develop symptoms because of the sudden onset of CHF, with marked dyspnea and weakness. Patients with chronic AR may remain asymptomatic for many years. Mild dyspnea on exertion and palpitations, especially on lying down, may occur. Exertional dyspnea, orthopnea, paroxysmal nocturnal dyspnea, fatigue, and edema are common clinical symptoms of LV failure. Syncope is rare. Angina pectoris occurs less often in patients with AR than in patients with AS and may be due to coexistent CAD. However, nocturnal angina pectoris, often accompanied by flushing, diaphoresis, and palpitations, may develop when the heart rate slows and the arterial diastolic pressure falls to very low levels. Most patients with severe AR who do not have surgery die within two years after CHF develops (98).

Signs

The AR murmur is typically a high-pitched blowing diastolic murmur that begins immediately after A2. The diastolic murmur is best heard along the left sternal border in the third and fourth intercostal spaces when AR is due to valvular disease. The murmur is best heard along the right sternal border when AR is due to dilatation of the ascending aorta. The diastolic murmur is best heard with the diaphragm of the stethoscope with the person sitting up, leaning forward, and holding the breath in deep expiration. The severity of AR correlates with the duration of the diastolic murmur, not with the intensity of the murmur.

Grayburn et al. (99) heard an AR murmur in 73% of 82 patients with AR and in 8% of 24 patients without AR. Saal et al. (100) heard an AR murmur in 80% of 35 patients with AR and in 10% of 10 patients without AR. Meyers et al. (101) heard an AR murmur in 73% of 66 patients with AR and in 22% of 9 patients without AR. Table 6 shows that an AR murmur was heard in 95% of 74 elderly patients with severe or moderate AR diagnosed by pulsed Doppler echocardiography, in 61% of 57 elderly patients with mild AR, and in 3% of 319 elderly patients with no AR (91).

In patients with chronic severe AR, the LV apical impulse is diffuse, hyperdynamic, and displaced laterally and inferiorly. A rumbling diastolic murmur (Austin Flint) may be heard at the apex, with its intensity decreased by inhalation of amyl nitrite. A short basal systolic ejection murmur is heard. A palpable LV rapid filling wave and an audible S3 at the apex are usually found. Physical findings due to a large LV stroke volume and a rapid diastolic runoff in patients with severe AR include a wide pulse pressure with an increased systolic arterial pressure and an abnormally low diastolic arterial pressure, an arterial pulse that abruptly rises and collapses, a bisferiens pulse, bobbing of the head with each heart beat, booming systolic and diastolic sounds heard over the femoral artery, capillary pulsations, and systolic and diastolic murmurs heard over the femoral artery when compressing it proximally and distally.

Table 6  Correlation of Aortic Regurgitation Murmur with Severity of AR in Elderly Patients with Chronic Aortic Regurgitation

<table>
<thead>
<tr>
<th>AR murmur (%)</th>
<th>AR murmur (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Severe or moderate AR (n = 74)</td>
<td>95</td>
</tr>
<tr>
<td>Mild AR (n = 57)</td>
<td>61</td>
</tr>
<tr>
<td>No AR (n = 319)</td>
<td>3</td>
</tr>
</tbody>
</table>

Abbreviation: AR, aortic regurgitation.
Source: Adapted from Ref. 91.
Electrocardiography and Chest Roentgenography

The electrocardiogram may initially be normal in patients with acute severe AR. Roberts and Day (102) showed in 30 necropsy patients with chronic severe AR that the electrocardiogram did not accurately predict the severity of AR or cardiac weight. Using various electrocardiographic criteria, the prevalence of LV hypertrophy varied from 30% (RV6 > RV5) to 90% (total 12-lead QRS voltage > 175 mm). The P-R interval was prolonged in 28% of patients, and the QRS duration was greater than or equal to 0.12 seconds in 20% of patients (102).

The chest X-ray in patients with acute severe AR may show a normal heart size and pulmonary edema. The chest X-ray in patients with chronic severe AR usually shows a dilated LV, with elongation of the apex inferiorly and posteriorly and a dilated aorta. Aneurysmal dilatation of the aorta suggests that aortic root disease is causing the AR. Linear calcifications in the wall of the ascending aorta are seen in syphilitic AR and in degenerative disease.

Echocardiography and Doppler Echocardiography

M-mode and two-dimensional echocardiography and Doppler echocardiography are very useful in the diagnosis of AR. Two-dimensional echocardiography can provide information showing the etiology of the AR and measurements of LV function. Eccentric LV hypertrophy is diagnosed by echocardiography if the LV mass index is increased with a relative wall thickness less than 0.45 (103–105). Echocardiographic measurements reported to predict an unfavorable response to AVR in patients with chronic AR include a LV end-systolic dimension greater than 55 mm (106), a LV shortening fraction less than 25% (106), a LV diastolic radius-to-wall thickness ratio greater than 3.8 (107), a LV end-diastolic dimension index greater than 38 mm/m² (2,107), and a LV ventricular end-systolic dimension index greater than 26 mm/m² (2,107).

Grayburn et al. (99) showed that pulsed Doppler echocardiography correctly identified the presence of AR in 57 of 57 patients (100%) with greater than or equal to 2+AR and in 22 of 25 patients (88%) with 1+AR. Saal et al. (100) demonstrated that pulsed Doppler echocardiography identified the presence of AR in 34 of 35 patients (97%) with documented AR. Continuous-wave Doppler echocardiography has also been shown to be very useful in diagnosing and quantitating AR (108,109). AR is best assessed by color flow Doppler imaging (110). Figure 6 illustrates two-dimensional echocardiographic and color Doppler findings in an elderly patient with chronic severe AR. Figure 7 illustrates continuous-wave Doppler findings in the elderly patient with chronic severe AR shown in Figure 6.

Natural History

The natural history of chronic AR is significantly different from the natural history of acute AR. Patients with acute AR should have immediate AVR because death may occur within hours to days. In one study of patients with hemodynamically significant chronic AR treated medically, 75% were alive at five years after diagnosis (52,111). Of patients with moderate to severe chronic AR, 50% were alive at 10 years after diagnosis (52,111). The 10-year survival rate for patients with mild to moderate chronic AR was 85% to 95% (52,112).
Figure 6 Two-dimensional echocardiographic image from an apical four-chamber view in an elderly patient with severe aortic insufficiency, showing a large diastolic aliasing color Doppler jet in the left ventricular outflow tract. *Abbreviations:* AI, aortic insufficiency; LV, left ventricular cavity; MV, mitral valve leaflets; LA, left atrium; RA, right atrium.
Figure 7 Continuous-wave Doppler recording of the velocity profile across the aortic valve in the same patient shown in Figure 6. A holosystolic decrescendo high-velocity profile is recorded from the left ventricular outflow tract, characteristic of aortic insufficiency.

Abbreviation: AI, aortic insufficiency.
Aortic Valve Disease in the Elderly

In another study of 14 patients with chronic severe AR who did not have surgery, 13 (93%) died within two years of developing CHF (98). The mean survival time after the onset of angina pectoris is five years (111).

During 8-year follow-up of 104 asymptomatic patients with chronic severe AR and normal LV ejection fraction, 2 patients (2%) died suddenly, and 23 patients (22%) had AVR (113). Of the 104 patients, 19 (18%) had AVR because of cardiac symptoms and 4 (4%) had AVR because of the development of LV systolic dysfunction in the absence of cardiac symptoms. Multivariate analysis showed that age, initial end-systolic dimension, rate of change in end-systolic dimension, and resting LV ejection fraction during serial studies predicted the outcome.

In a prospective study, at 24-month follow-up (range, 7–55 months) of 17 patients, mean age 83 years, with CHF associated with unoperated severe chronic AR and a normal LV ejection fraction, 15 patients (88%) were dead (95). At 15-month follow-up (range, 8–21 months) of eight patients, mean age 85 years, with CHF associated with unoperated severe chronic AR and an abnormal LV ejection fraction, all of them (100%) were dead (95).

Medical and Surgical Management

Asymptomatic patients with mild or moderate AR do not require therapy. However, prophylactic antibiotics should be used to prevent bacterial endocarditis in patients with AR, according to AHA guidelines (65). Echocardiographic evaluation of LV end-systolic dimension should be performed yearly if the measurement is less than 50 mm, but at every three to six months if the LV end-systolic dimension is 50 to 54 mm. AVR should also be considered when the LV ejection fraction approaches 50% before the decompensated state (92).

Patients with asymptomatic, chronic severe AR have been treated with hydralazine (114), nifedipine (115), or angiotensin-converting enzyme therapy (116) to decrease the LV volume overload. Vasodilator therapy is indicated as chronic therapy in patients with severe AR who have symptoms of an abnormal LV ejection fraction when AVR is not recommended because of additional cardiac or noncardiac factors (class I indication) and as short-term therapy to improve the hemodynamic profile of patients with severe CHF symptoms and severe LV systolic dysfunction before proceeding with AVR (class IIa indication) (64). Long-term vasodilator therapy with enalapril or nifedipine did not reduce or delay the need for AVR in patients with asymptomatic severe AR and normal LV ejection fraction (117).

Infections should be treated promptly. Systemic hypertension increases the regurgitant flow and should be treated. Drugs that depress LV function should not be used. Arrhythmias should be treated. Patients with AR due to syphilitic aortitis should receive a course of penicillin therapy. Prophylactic resection should be considered in patients with Marfan’s syndrome when the aortic root diameter exceeds 55 mm (118).

Bacterial endocarditis should be treated with intravenous antibiotics. Indications for AVR in patients with AR due to bacterial endocarditis are CHF, uncontrolled infection, myocardial or valvular ring abcess, prosthetic valve dysfunction or dehiscence, and multiple embolic episodes (119–121).

CHF should be treated with sodium restriction, diuretics, digoxin if the LV ejection fraction is abnormal, vasodilator therapy, and AVR. Angina pectoris should be treated with nitrates.

Patients with acute severe AR should undergo AVR immediately. Patients with chronic severe AR should have AVR if they develop symptoms of CHF, angina pectoris, or syncope (64,113). AVR should also be performed in asymptomatic patients with chronic severe AR if their LV ejection fraction is less than or equal to 50% at rest.
Table 7. ACC/AHA Class I Indications for Aortic Valve Replacement in Persons with Chronic Severe AR

1. Symptomatic patients with severe AR and normal or abnormal LV ejection fraction
2. Asymptomatic patients with severe AR and LV ejection fraction ≤50% at rest
3. Patients with severe AR undergoing coronary artery bypass surgery or surgery on the aorta or other heart valves
4. Asymptomatic patients with severe AR with LV ejection fraction >50% but a LV end-diastolic dimension >75 mm or a LV end-systolic dimension >55 mm (class IIa indication)

Abbreviations: ACC/AHA, American College of Cardiology/American Heart Association; LV, left ventricular; AR, aortic regurgitation.
Source: Modified from Ref. 64.

(64,113). Table 7 shows three class I and one class IIa ACC/AHA indications for AVR in patients with chronic severe AR (64). The class I indications for AVR include symptoms with an abnormal or normal LV ejection fraction, no symptoms but a LV ejection fraction less than or equal to 50% at rest, and asymptomatic patients undergoing CABG or surgery on the aorta or other heart valves (64). The class IIa indication for AVR is asymptomatic patients with severe AR with a LV ejection fraction greater than 50% but a LV end-diastolic dimension greater than 75 mm or a LV end-systolic dimension greater than 55 mm (64).

Elderly patients undergoing AVR for severe AR have an excellent postoperative survival if the preoperative LV ejection fraction is normal (122–124). If LV systolic dysfunction was present for less than one year, patients also did well postoperatively. However, if the person with severe AR has an abnormal LV ejection fraction and impaired exercise tolerance and/or the presence of LV systolic dysfunction for more than one year, the postoperative survival is poor (122–124). After AVR, women exhibit an excess late mortality, suggesting that surgical correction of severe chronic AR should be considered at an earlier stage in women (125).

The operative mortality for AVR in elderly patients with severe AR is similar to that in elderly patients with AVR for valvular AS. The mortality rate is slightly increased in patients with infective endocarditis and in those patients needing replacement of the ascending aorta plus aortic valve replacement.

Of 450 patients with severe AR, 273 (61%) had a LV ejection fraction greater than or equal to 50%, 134 (30%) had a LV ejection fraction of 35% to 50%, and 43 patients (10%) had a LV ejection fraction less than 35% (126). The operative mortality was 3.7% for patients with a normal LV ejection fraction, 6.7% for patients with a LV ejection fraction of 35% to 50%, and 14% for patients with a LV ejection fraction less than 35% (126). At 10-year follow-up, survival rates were 70% for patients with a normal LV ejection fraction, 56% for patients with a LV ejection fraction of 35% to 50%, and 41% for patients with a LV ejection fraction less than 35% (126).

The bioprosthesis is preferable to the mechanical prosthetic valve for AVR in elderly patients with severe AR as in elderly patients with valvular AS (68,69). Patients with porcine bioprostheses may be treated with antiplatelet therapy alone unless they have AF, abnormal LV ejection fraction, previous thromboembolism, or a hypercoagulable state (64).

In a prospective study, AVR in 38 patients with severe AR normalized LV chamber size and mass in two-third of patients undergoing surgery (127). At nine-month follow-up after AVR, 58% of patients had a normal LV end-diastolic dimension, and 50% of patients had a normal LV mass. During further follow-up (18–56 months postoperatively) 66% of patients had a normal LV end-diastolic dimension and 68% of patients had a
normal LV mass. The LV end-diastolic dimension normalized in 86% of patients with a preoperative LV end-systolic dimension less than or equal to 55 mm. A preoperative LV end-systolic dimension greater than 55 mm was present in 81% of patients with postoperative persistent LV dilatation (127).

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Mitral Regurgitation, Mitral Stenosis, and Mitral Annular Calcification in the Elderly

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**ETIOLOGY**

**Mitral Stenosis**

The etiology of mitral stenosis (MS) in the elderly as in the young patient is chronic rheumatic heart disease. There is a small incidence of mitral annular calcification with exuberant atherosclerotic encroachment from the annulus into the base of the left ventricle such that the mitral orifice is decreased, producing some degree of mitral stenosis, most often not severe. Reduced anterior leaflet mobility seems to be necessary to produce obstruction sufficient for a gradient of greater than 5 mmHg (1).

With the marked decrease in the incidence of acute rheumatic fever in the United States over the last half century, the prevalence of MS in those people under age 40, born and raised in the United States with chronic rheumatic heart disease and MS or mitral regurgitation has markedly decreased, so that MS in this population is seen predominantly in the elderly patient, frequently the older patient who has had earlier mitral valve surgery. Since rheumatic fever is still very common in eastern Europe, Asia, Latin and South America, and Africa, most of the younger patients with MS in the United States were born and raised in these countries.

**Mitral Regurgitation**

In the elderly patient mitral valve disease, especially mitral regurgitation (MR), is more frequently seen than aortic valve disease, although aortic stenosis is much more often the reason for valve surgery in this age group (2). MR has numerous etiologies (Table 1) (3). The most frequent etiologies in elderly patients are myxomatous degeneration (mitral...
valve prolapse), functional MR due to left ventricular dilatation, coronary artery disease, rheumatic heart disease, and mitral annular calcification. Since mitral annular calcification is seen predominantly in the elderly patient and poses problems beyond those related to volume overload, a detailed discussion of this topic will be presented separately at the end of the chapter.

Anorexogenic drugs (fenfluoramine) possibly related to serotonergic medications that are agonists at the 5-hydroxytryptamine (2B) (5-HT 2B) receptor. Have been shown to produce valvulopathy similar to that seen in carcinoid valve disease (4,5). Recently, ergot-derived dopamine receptor agonists (pergolide, cabergoline) often used in Parkinson’s disease have been associated with increased risk of valvular regurgitation (6).

PATHOPHYSIOLOGY

MS

The major pathology is that of commissural fusion and fusion and shortening of the chordae tendinae. Later, there is increasing fibrosis and calcification of the valve leaflets. Therefore, the obstruction to diastolic flow across the mitral valve can be due to the narrowed mitral orifice caused by commissural fusion and to the thickening and calcification of the leaflets, so that they do not open without a pressure gradient in spite of open commissures or obstruction due to a subvalvular component caused by fused, shortened chordae tendinae. In these latter two instances, commissurotomy will not relieve the obstruction and valve replacement is necessary.

The normal mitral valve orifice is approximately 5.0 cm². With a normal stroke volume there is no obstruction to diastolic flow until the valve area is reduced to approximately 2.0 cm². When the valve area reaches about 1.0 cm², there is sufficient

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**Table 1** Etiologies of MR

| 1. Rheumatic heart disease |
| 2. Mitral valve prolapse (myxomatous degeneration) |
| 3. Infective endocarditis |
| 4. Left ventricular dilatation (left ventricular failure) |
| 5. Idiopathic rupture of chordae tendinae |
| 6. Trauma, penetrating and nonpenetrating |
| 7. Coronary artery disease |
| a. Transient ischemia |
| b. Myocardial infarction |
| c. Ruptured papillary muscle |
| 8. Connective tissue diseases (lupus erythematosus, Marfan disease) |
| 9. Mitral annular calcification |
| 10. Postmitral valvotomy |
| 11. Valve dehiscence |
| 12. Paraprosthetic MR |
| 13. Degeneration of a bioprosthetic valve |
| 14. Drug associated valvulopathy (fenfluoramine, pergolide) |

*Etiologies where clinical picture may be that of acute MR. Abbreviation: MR, mitral regurgitation.*
obstruction at resting flow rates to result in a diastolic gradient across the mitral valve, so the left atrial pressure as well as pulmonary venous and pulmonary capillary pressures rise enough to cause pulmonary congestive symptoms (7).

The obstruction and pressure gradient between the left atrium and left ventricle in diastole accelerates the blood through the narrowed orifice, causing the turbulence and vortex formation that generates the characteristic low-frequency diastolic murmur. The loudness of the murmur is related to the magnitude of the pressure gradient and to the volume of blood accelerated across the obstructed valve as well as to the nearness of the chamber in which the murmur is generated (here the left ventricle) to the ear. Since the left ventricular apex pushes the chest wall in systole creating the point of maximal impulse (PMI), this is where the murmur is best heard.

As left atrial pressure rises, pulmonary capillary pressure rises and overcomes the colloid osmotic pressure in the pulmonary capillary bed, leading to increasing congestion in the interstitial areas of the lung and finally to pulmonary edema. As left atrial pressure rises, there is a pari passu rise in right ventricular systolic pressure, increasing afterload on the right ventricle, right ventricular hypertrophy, and finally resulting in right ventricular failure. In 10% to 15% of cases there is a marked increase in pulmonary artery pressure and pulmonary vascular resistance due to edema pressure on the interstitial small arteries and vasoconstriction probably mediated by pulmonary artery endothelial release of vasoconstrictive amines such as endothelin. Eventually, with right ventricular failure, there is a decrease in cardiac output, and signs of right ventricular failure with increased central venous pressure, edema, and even ascites (7).

As left atrial pressure rises, the left atrium enlarges resulting in atrial fibrillation (AF) that may occur relatively early in the course of MS. With AF, stasis of blood, especially in the left atrial appendage, as well as endocardial changes (8) that promote platelet activation and release of thrombogenic substances result in atrial clotting and form the basis for the high incidence of systemic thromboemboli, the most important of which is embolic stroke that is so common in MS (9).

Hemoptysis occurs in these patients as pulmonary venous pressure increases, opening collaterals for run-off to the bronchial veins. These protrude into the lumen of the bronchi and, when rupture occurs, cause hemoptysis (7). Ortner’s syndrome (paralysis of the left vocal cord) can occur with the recurrent laryngeal nerve, which hooks around the ligamentum arteriosus being stretched by the enlarging left pulmonary artery and left atrium (10).

MR

Mechanism of Regurgitant Orifice Formation

The development of MR depends on the formation during systole of a regurgitant orifice. There are a number of mechanisms by which this can occur. Dilatation of the left ventricular OS (including the mitral annulus) is seen in any cause of ventricular failure with left ventricular dilatation. The valve itself remains normal, but the area of the mitral opening is too great to be closed by coaptation of the leaflets. There is also displacement of the papillary muscles and more lateral tension in systole on the leaflet edges, thus restricting leaflet motion (11). A similar problem occurs with ischemia and myocardial fibrosis where the mural leaflet is held from coapting with the anterior leaflet. Other mechanisms of regurgitant orifice formation are loss of leaflet tissue and fibrosis, retraction of leaflet tissue as is seen in rheumatic heart disease, or tearing of the leaflet as in infective endocarditis, seen also in penetrating and nonpenetrating trauma. Finally, there can be loss of infravalvular support as seen in chordal and papillary muscle rupture.
With myxomatous leaflets, mitral valve prolapse occurs where there may be coaptation of the leaflets early in systole, but as the left ventricle empties and becomes smaller, the redundant leaflet is displaced back above the mitral annulus into the left atrium, and at some point a regurgitant orifice is created (12). With myocardial infarction and fibrosis of the papillary muscle and its origin from the left ventricular wall, as systole progresses, the mitral valve leaflets prolapse toward the left atrium and a regurgitant orifice forms. With annular calcification, the OS of the left ventricle is prevented from constricting during systole and the mural leaflet can be immobilized, preventing it from coapting with the anterior leaflet.

**Pathophysiology Causing Symptoms**

**Acute MR.** The pathophysiology of MR depends on the severity of the leak (regurgitant volume) and the rapidity with which the MR occurred. With sudden chordal or leaflet rupture or valve dehiscence, a sudden low-resistance runoff in systole from the left ventricle develops. If the regurgitant orifice is large, the regurgitant volume will be large. The total left ventricular stroke volume is now divided into the stroke volume going out of the aorta (effective forward stroke volume) and the blood regurgitating back into the left atrium (regurgitant volume). The left ventricle in this situation empties rapidly during systole. Since much of the regurgitant volume goes into the left atrium against low resistance, the left ventricle faces a decreased afterload early in systole, permitting it to empty more easily and achieving a smaller end-systolic volume and a higher ejection fraction (EF) (7).

The increased blood coming into the left atrium during systole results in a higher “V” wave. With the next diastole, the blood coming from the pulmonary veins adds to the regurgitant blood thus increasing the left ventricular end-diastolic volume (LVEDV). The Frank–Starling mechanism increases the next left ventricular stroke volume so that the regurgitant volume can be maintained as well as the effective forward stroke volume. In acute MR, the sudden increase in LVEDV, resisted by the unprepared left ventricle and unstretched pericardium, results in a marked rise in left ventricular filling pressure. With the increased filling pressure the left atrial and pulmonary capillary pressure is increased causing pulmonary congestion and pulmonary edema. With the rise in left atrial pressure there is a sudden increase in afterload on the right ventricle, which may dilate and rapidly fail (7).

**Chronic MR.** With gradually increasing regurgitant volume, there is stimulus and time for remodeling of the left ventricle and eccentric hypertrophy to occur. As the ventricle dilates, left ventricular hypertrophy (LVH) occurs so that the wall does not become thinner, preventing an increase in left ventricular wall tension. The ventricle remains compliant and the pericardium stretches to keep the left ventricular filling pressure and the left atrial pressure normal. The dilated more compliant left atrium limits the height of the “V” wave to 30 to 35 mmHg. The left ventricular filling pressure remains normal until the left ventricle fails, at which time the filling pressure rises.

Since the left ventricle is contracting against a lower afterload, the EF remains normal or even higher than normal. As the left ventricular end-diastolic diameter increases, eventually the wall tension and afterload increases and the EF begins to fall (13). At this stage, even with the EF still “within normal limits,” there is a decrease in myocardial contractility. When the left atrial mean pressure rises, there is increased afterload on the right ventricle, which eventually leads to right ventricular failure. Here, right ventricular failure is very late in the course of the natural history.
Age modifies the pathophysiology of MR. In the elderly there is decreased compliance of the left ventricle (14) as well as LVH, which leads to a further, more rapid increase in left ventricular filling pressure given the volume load present in MR. With the increased aortic stiffness present in the elderly (15), there is increased left ventricular impedance to ejection and increased left ventricular afterload leading to earlier decompensation of the left ventricle in MR.

CLINICAL PICTURE

MS

Symptoms
For many years, the patient may remain asymptomatic. In the elderly, many patients have had a previous intervention, either surgical or balloon valvotomy. In elderly patients, pulmonary congestion almost always results in progressive dyspnea on exertion and eventually orthopnea and paroxysmal nocturnal dyspnea. Wall tension and enlargement of the left atrium lead to the development of AF and the increased danger of systemic emboli, especially stroke (7). Frequently the first symptoms occur with the onset of AF or, in the young patient, during the course of pregnancy, usually in the late second or third trimester (7). With decreasing right ventricular function, the patient may have fewer symptoms and signs of pulmonary congestion and more problems with decreased exercise tolerance. Eventually, the clinical picture is dominated by the signs and symptoms of right heart failure, pedal edema, engorged neck veins, and finally ascites and the stasis cyanosis of low cardiac output.

Signs
The murmur of MS is a characteristic low-pitched, rumbling diastolic murmur best heard at the apex. With flexible valve leaflets, the first heart sound is loud and even palpable and there is an opening snap after the S2 in early diastole. The second heart sound may be increased and even palpable if the pulmonary artery pressure is elevated. With severe pulmonary hypertension, a diastolic blowing murmur of pulmonic insufficiency may be heard along the left-sternal border, indistinguishable from the murmur of aortic regurgitation (Graham–Steele murmur). With right ventricular hypertrophy, there may be a precordial lift. With right heart failure, a systolic murmur along the left sternal border of tricuspid regurgitation may be present, as well as an elevated central venous pressure, hepatomegaly, edema, and even ascites (7).

Age Modifies Signs and Symptoms of MS
In the elderly, symptoms of MS may be far advanced before the patient recognizes them. Elderly patients may accept shortness of breath and decreased exercise tolerance as an inevitable consequence of “getting older.” Also, accompanying comorbidities, such as chronic obstructive pulmonary disease, may be accepted as the cause of the increasing symptoms. In the elderly patient, the antero-posterior (AP) diameter of the chest is frequently increased so that the left ventricle no longer contacts the chest wall. Also, dilatation of the right ventricle may move the left ventricle posteriorly away from contact with the chest wall. Since the low-frequency murmur does not conduct well through the blood of the right ventricle, the murmur may be inaudible (7). Sometimes rolling the patient into the left lateral position can bring the left ventricle into contact with the chest wall.
wall and make the murmur detectable with the bell of the stethoscope over the point of maximal impulse. Also, increasing the heart rate and cardiac output with exercise increases the diastolic gradient across the mitral valve and makes the murmur louder.

Since the elderly are more likely to have a fibrotic, calcified valve, the first heart sound may not be loud and the opening snap may be absent. In these patients the MS may be truly silent and the patient simply looks like a patient of heart failure.

Laboratory Findings and Diagnosis
The classic findings on a chest X-ray are those of right ventricular dilatation, prominence of the pulmonary artery and pulmonary veins, especially with redistribution to the upper lung fields. There is also a double density behind the right cardiac silhouette protruding beyond the right heart border of left atrial enlargement, and a filling in below the main pulmonary artery segment in the AP view of the left atrial appendage. In the lateral film, at times, calcification of the mitral valve can be seen, but can be observed better on fluoroscopy.

The classic findings on electrocardiogram (ECG) are left atrial abnormality and right ventricular hypertrophy. In the elderly, AF is common.

The restricted opening of the mitral valve can be seen in the 2-D echocardiogram and the mitral orifice can be planimetered. The increased diastolic velocity across the mitral valve is measured by Doppler echocardiography and the diastolic gradient is calculated by the formula (16)

$$\text{Gradient} = 4V^2$$

The severity of the MS can be calculated from the diastolic half-time (17) and the mitral orifice area from the continuity equation (18)

$$\text{Mitral valve area} = \frac{\text{LV outflow tract area} \times \text{velocity}}{\text{Velocity across mitral valve}}$$

or by the proximal isovelocity surface area (PISA) method (19)

$$\text{Mitral area} = \frac{\text{Flow} \times (2\pi r^2)}{\text{Velocity across mitral valve}}$$

where $r$ is determined from the Nyquist limit.

There are several echocardiographic scores (20,21), which by looking at the thickness and mobility of the leaflets, the degree of leaflet and commissural calcification, and subvalvular chordal fusion, can reliably identify those patients who will benefit from balloon or surgical valvotomy and those who should have valve replacement. Other imaging techniques such as magnetic resonance imaging (MRI) and computed angiographic tomography (CAT) scanning can demonstrate the pathophysiologic abnormalities in MS but generally do not contribute significantly to the more common laboratory studies and therefore are not generally used.

MR
Symptoms
Acute MR. With sudden development of severe MR, there is no time for compensatory eccentric hypertrophy or enlargement of the left atrium, so the patient frequently develops severe shortness of breath, orthopnea, paroxysmal nocturnal dyspnea (PND), early pulmonary edema, and even right heart failure. Since the left atrium is not dilated, it is unusual for the patient to be in AF (22).
Chronic MR. The patient may remain asymptomatic for years. Eventually the earliest symptom may be a decrease in exercise tolerance rather than dyspnea on exertion since with left ventricular dysfunction the forward stroke volume may decrease with exercise. Later shortness of breath, orthopnea, PND, and left heart failure occur. Finally, right heart failure is very late in the course of the disease (23).

The elderly patient may deny symptoms thinking that decreased exercise tolerance is due to aging and shortness of breath is due to pulmonary disease. Also, with a gradual decrease in the patient’s ability to exercise, symptoms may be avoided by decreasing the level of activity so that the patient may have very severe MR and still deny symptoms.

Signs

Acute MR. With acute MR the perioperative myocardial infarction (PMI) may not be displaced but is hyperactive, especially compared with the radial pulse, and may be rapid rising and abbreviated. If the regurgitant orifice is very large, pressure in the left atrium and left ventricle may approach equality, in which case the murmur may be short or even absent. These patients are usually extremely dyspneic or in pulmonary edema (22). With posterior leaflet prolapse, the regurgitant jet may be directed anteriorly and superiorly so that the murmur may be heard well at the base as well as at the apex. With anterior leaflet prolapse, the jet is directed posteriorly and is well heard in the back.

The murmur of acute MR may be confused with that of aortic stenosis but with a premature ventricular contraction, the postextrasystolic beat results in a murmur that does not get louder, unlike that of the postextrasystolic beat in aortic stenosis. With rapid filling of the left ventricle, there is frequently an S₃, and since the rhythm is usually sinus rhythm, an S₄.

Chronic MR. With chronic MR, the left ventricle is dilated and the PMI is displaced laterally and sustained. With the PMI and carotid pulse felt simultaneously, instead of the PMI collapsing before the carotid pulse, with LVH the PMI collapses after the carotid pulse. The pansystolic murmur of MR, best heard at the apex, is flat throughout systole.

Since the regurgitation continues throughout all of left ventricular systole, there are no isovolumic contraction or relaxation phases and the murmur classically buries the first and second heart sounds (23). In patients where the regurgitant orifice does not form until the ventricle is ejecting, such as in mitral valve prolapse, nonejection click or clicks may be present as the leaflet prolapses and is suddenly stopped in its motion. Since the regurgitant orifice continues to enlarge as the ventricle empties, the murmur starts after the click, crescendos in loudness, and incorporates the second sound (24).

With the marked increase in diastolic blood flow across the mitral valve, there may be a short diastolic rumble and an S₃ sound. AF is common in the elderly patient with significant MR.

Other signs and symptoms may be related to the etiology of the MR. For instance, with MR secondary to a dilated left ventricle, the findings of cardiomyopathy may be present with an S₃ and S₄ gallop. Fever and immunoembolic signs may be present in patients with infective endocarditis, physical signs of connective tissue diseases such as Marfan disease, or a history of trauma, angina, or acute myocardial infarction.

Laboratory Findings and Diagnosis

Chest X-ray. Since there is no time for atrial or ventricular remodeling, in acute MR the heart may not be enlarged on the chest X-ray. Pulmonary congestion and edema are commonly seen. With chronic severe MR, the left atrium and ventricle are dilated and
appear enlarged on the chest X-ray. With chronic MR, occasionally the left atrium can become extremely dilated so that it touches the right lateral chest wall compressing the right lower lung.

**ECG.** With acute MR, the ECG may be normal, except for sinus tachycardia, or have only nonspecific ST-T-wave changes. With chronic MR, LVH, left atrial abnormality, and AF are common.

**Echocardiography.** The regurgitant volume and size of the regurgitant orifice can be estimated by Doppler echocardiography. The effect of the MR on the size and function of the cardiac chambers can also be evaluated. With acute severe MR, there is frequently pulmonary hypertension, which can be estimated by identifying a tricuspid regurgitant jet that allows estimation of the pulmonary artery systolic pressure (25). The direction of the MR regurgitant jet as well as multiple views on transesophageal echocardiogram (TEE) can reliably show which scallops of the mitral leaflets are prolapsing and define the anatomical and functional mechanism causing the MR; and it is necessary for planning the surgical procedure (26).

The severity of MR is more difficult to quantitate than the severity of MS. By Doppler echocardiography, the regurgitant jet by color-flow mapping is composed of a roughly hemispherical area of flow convergence resulting from serial aliasing (PISA), the regurgitant orifice and the fully developed regurgitant jet. Multiple measurements have been used to quantitate the magnitude of MR. The jet area in proportion to the left atrial area, the width of the jet at the regurgitant orifice, the calculated regurgitant volume, the intensity of the continuous-wave MR signal, the mitral inflow/pulmonary vein Doppler signs have all been used. Using PISA, it is possible to calculate the regurgitant volume and the effective orifice area. These measurements should be the best estimate of regurgitant severity, although the accuracy of the flow rate by this method depends on many variables such as the shape of the PISA, the orifice geometry, aliasing velocity and others (27).

Thomas and colleagues (28) developed an MR index using six echo-Doppler findings, three related to the regurgitant volume and three to the effect on the cardiac chambers. The index correlated well with regurgitant fraction and other measures of MR severity and identified patients with severe MR with a 90% sensitivity, a 88% specificity, and a 79% positive predictive value.

As in the case of MS, the imaging techniques of MRI and CAT scanning can demonstrate similar pathophysiologic abnormalities, but are generally not used clinically.

**NATURAL HISTORY OF MS AND MR IN THE ELDERLY**

**MS**

A patient over age 65 with MS who has not already had a commissurotomy will have had mild MS for many years, or may have progressed to moderate MS. Others have progressed to severe MS by valvular fibrosis and calcification. Many have had MS diagnosed at an early age and, if symptomatic, had a valvotomy or valve replacement.

Once MS becomes symptomatic, the course usually is to become progressively more symptomatic, going through the pulmonary congestive phase, then the right heart failure phase, and finally the low-cardiac-output stage leading to death (7). Since valvotomy or valve replacement has been available for over half a century, it is unusual to see an elderly person with severe MS who has not had at least one attempt at valvotomy.
Mainly in newly arrived patients in the United States do we see the elderly with previously unrecognized severe MS.

MR

The natural history of patients with MR depends on the acuteness of onset, severity, and etiology of MR. The presence of echocardiographic MR early after acute myocardial infarction is predictive of decreased survival. The prevalence of MR increases with age, diabetes, hypertension, and previous revascularization. However, mild or moderate MR may not be an independent prognostic predictor (28). In patients who have decreased ventricular function or heart failure after an acute myocardial infarction, increased MR at baseline was associated with larger LVEDV and left ventricular end-systolic volume, increased sphericity index, and reduced EF. Moderate to severe MR is an independent predictor of total mortality, cardiovascular mortality, and hospitalization for heart failure on follow-up. If the severity of the MR progresses during the first post-myocardial infarction month, patients are likely to die or develop heart failure (29). With MR caused by ischemia or myocardial infarction, the prognosis is poor unless there is minimal myocardial damage and the ischemic muscle can be revascularized and the valve made competent (30). With endocarditis the cause of the MR, the course depends on the infecting organism and the complications seen with infective endocarditis. If trauma is the etiology, the damage to the heart and other organs determines the course.

Acute MR

How large the regurgitant volume is when the acute MR occurs will determine the symptomatic state of the patient. In the elderly patient, the stiffer left ventricle results in a higher filling pressure for a given volume overload. With a single chord rupture, there may be minimal to moderate regurgitation and the patient may not exhibit the clinical picture of acute MR. With the rupture of several primary chords or of the papillary muscle tip, the patient exhibits the classic clinical picture of acute MR and frequently presents with pulmonary edema, culminating in early demise (22).

With the decrease in afterload, the ventricle empties in systole to a greater extent than normal and the EF increases. With myocardial dysfunction, the left ventricular end-diastolic and end-systolic volumes increase and the EF begins to fall, at times into the normal range (13). The decrease in EF in this case still identifies myocardial dysfunction that has a negative effect on prognosis even after surgical correction of the MR (31). Although in one study a relatively high incidence of sudden death has been reported in patients with acute MR due to flail leaflets (32), it has not been confirmed because in that study coronary artery disease could not be ruled out as the etiology. (33).

After a period of time, remodeling of the left atrium and left ventricle allows the filling pressure to fall and the effective forward stroke volume to be maintained. The patient may become less symptomatic and the clinical picture may become that of chronic MR.

Chronic MR

Patients with chronic MR can remain asymptomatic for many years with good exercise tolerance (34). At some point, the volume load on the left ventricle combined with increasing afterload due to the ventricle becoming more spherical and increasing its radius results in myocardial dysfunction. The course becomes that of increasing symptoms and death, usually from congestive heart failure (23).
TREATMENT OF MS AND MR IN THE ELDERLY

MS

Balloon Valvotomy for MS

In elderly patients with mild-to-moderate MS who have good or acceptable exercise tolerance consistent with their age and not interfering with their life, controlling volume overload, the ventricular rate if in AF, and anticoagulation with warfarin because of the high risk of systemic embolization is the best approach. If the patient develops symptoms that do not respond to gentle diuresis and rate control with β blockers or calcium channel blockers, valvotomy should be considered. If the valve is flexible, with minimal calcification, no left atrial thrombus, and no more than mild (grade 2 or less) MR, the patient is a candidate for valvotomy (35). Commissural calcification has an adverse effect on the results of balloon valvotomy with smaller increases in mitral valve area as calcification increases and a smaller reduction in functional class after balloon mitral valvotomy (36). At the present time with experienced operators, balloon valvotomy is the treatment of choice rather than open commissurotomy (37,38). With balloon valvotomy, the success rate of increasing the valve area to 1.5 cm² or greater, effectively doubling the valve area, is high—about 90%, even in valves with a high echo score (39). Preexisting MR is a risk factor predicting poor outcome (39,40). The presence of commissural calcium is related to the development of MR after balloon valvotomy, and with calcification of the valve there is less chance that the valve can be opened to greater than or equal to 1.5 cm² and less improvement in symptoms.

Iung and colleagues (41) reported results of balloon valvotomy in 1514 patients, 45 ± 15 years of age. Twenty-five percent had calcified valves. A good result, defined as opening the mitral valve to 1.5 cm² or more without creating 2 + or greater MR, was obtained in 1348 (89%) patients. Important predictors of a good result were younger age, echo score less than or equal to 8, and relatively large predilation valve area. Palacios and colleagues (38) reported 327 patients with balloon valvotomy. There were seven in-hospital deaths. The follow-up period was 26 ± 12 months. The echo score, which evaluates the anatomical suitability for valvotomy using the Wilkins scoring system (20), was determined. Patients with an echo score greater than 8 compared with those less than or equal to 8 were older (64 ± 11 years vs. 48 ± 14 years) had more AF (65% vs. 40%), more valve calcification (81% vs. 29%) and more previous surgical commissurotomy (30% vs. 16%). Event-free survival was 79 ± 10% for those with echo score less than 8 versus 39 ± 18% with echo score greater than or equal to 8.

There is limited experience with valvotomy in patients over ages 60 to 70. Remadi and colleagues (42) reported the immediate and late outcomes of balloon mitral valvotomy in 745 patients, 45 of whom were aged 60 years or older. They compared the immediate and late outcomes with those below 60 years. The baseline hemodynamic parameters were comparable in the two groups as was the degree of mitral valve opening and favorable hemodynamic response. Complication rates, including the development of grade I and II MR, were also similar. After a mean of 43 months of follow-up, a good result was maintained in 60% of patients, even though some degree of restenosis occurred in 40% of the older patients, compared to 25% of the younger patients. Le Feuvre and colleagues (43) reported 234 patients who had a balloon valvotomy, only 28 (10%) aged 70 years or older. Compared to younger patients, the 70 years and older patients had a higher percentage of New York Heart Association (NYHA) class III and IV (84% vs. 67%), and higher echo scores (9.3 ± 2.1 vs. 8.0 ± 1.6), meaning they were less suitable for valvotomy. They also had more AF (61% vs. 36%), more complications (27% vs. 9%),
and a higher 30-day mortality (12% vs. 0.8%). The success rate in opening the valve was similar in both groups.

Long-term survival without cardiac events (death, cerebrovascular accidents, another intervention) depends on the patient’s age as well as comorbidity. In general, the older the patient and the more the comorbidity, the shorter the survival.

Meneveau and colleagues (44) reported 532 patients after balloon valvotomy (Table 2). The event-free survival was age dependent. The anatomical form of the mitral valve was the second important factor in event-free survival. Given the fact that a calcified valve is unfavorable for valvotomy, in those very symptomatic patients with calcified valves believed to be too great a risk for surgery, balloon valvotomy can be palliative, achieving a moderate increase in valve area at low procedural risk and with improvement of symptoms in the majority of patients. (45). Patients with echo scores that make them unsuitable for balloon valvotomy and rejected for surgery because of frailty or comorbidity can benefit from balloon valvotomy. Sutaria and colleagues (46) reported 80 patients over 70 years of age. Fifty-five were considered unsuitable for surgery. There was a 95% success rate in opening the valve. One year later, 28 of the 55 unsuitable patients (51%) had improved at least one NYHA Class and 14 (25%) at five years. Of the 25 with suitable valves, 16 (64%) had achieved this outcome at one year and 9 (36%) at five years. Shaw and colleagues (47) reported similar results in 20 patients 70 years of age and older. The absence of commissural calcification is a significant predictor of the frequency of achieving a mitral valve opening of 1.5 cm² without creating severe MR. Sutaria and colleagues (48) reported that calcification of one or more commissures predicts a less than 50% chance of achieving a valve area of greater than or equal to 1.5 cm². Its influence is greatest in valves with an echo score of less than or equal to 8. Those with commissural calcification grade of 0/1 had a significantly larger number of patients with improvement in symptoms and achieving a valve area of 1.5 cm² (67%) than those with a grade of 3/4 (46%). (48). If the echo score is greater than 8, the degree of commissural calcification is less important.

In patients age 80 and older, there is limited experience of balloon valvotomy. Sutaria and colleagues (49) reported 20 octogenarians (age range 80 to 89) with balloon valvuloplasty, all functional class II to IV, and 14 among them were unfit for surgery. The mitral valve area was increased by 106% from 0.81 ± 0.3 cm² to 1.67 ± 0.8 cm². Eight

<table>
<thead>
<tr>
<th>Table 2</th>
<th>Long-Term Follow-Up of 532 Patients with Balloon Valvotomy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Event-free survival</td>
<td>3 yr</td>
</tr>
<tr>
<td>Entire group</td>
<td>84%</td>
</tr>
<tr>
<td>Age ≤65</td>
<td>80%</td>
</tr>
<tr>
<td>Age &gt;65</td>
<td>52%</td>
</tr>
<tr>
<td>The anatomical form of the mitral valve was the second important factor in event-free survival</td>
<td></td>
</tr>
<tr>
<td>3 yr</td>
<td>5 yr</td>
</tr>
<tr>
<td>Favorable anatomy (echo score of 1)</td>
<td>92%</td>
</tr>
<tr>
<td>Intermediate anatomy (echo score of 2)</td>
<td>86%</td>
</tr>
<tr>
<td>Unfavorable anatomy (echo score of 3)</td>
<td>45%</td>
</tr>
</tbody>
</table>

Source: From Ref. 44.
patients attained a valve area of greater than or equal to 1.5 cm$^2$ and 16 an area greater than or equal to 1.2 cm$^2$. Eighty percent improved at least one NYHA functional class.

Since many elderly patients with MS have had a previous surgical commissurotomy, the question arises whether balloon valvotomy could be successful if restenosis occurs. Jung and colleagues (50) reported the results of balloon valvotomy in 232 patients, mean age 47 ± 14 years, who had undergone a surgical commissurotomy 16 ± years before. Eighty-one of these patients had valve calcification and bilateral commissural fusion. One patient died (0.4%), MR > 2/4 developed in 4% and 82% achieved an immediate valve area of greater than or equal to 1.5 cm$^2$ without significant MR. Predictors of a poor result were age ($p < 0.001$), smaller initial valve area ($p = 0.01$), and use of a double-balloon technique ($p = 0.015$), indicating that results in the elderly would not be as good. In the 175 patients with follow-up, eight-year survival without operation and in NYHA class I and II was 48 ± 5% and in those with good immediate results, 58 ± 6%.

The question of whether balloon valvotomy in the patient with MS or in the patient in normal sinus rhythm will prevent the later development of AF addresses the argument that early commissurotomy is necessary this complication. Eid Fawzy and colleagues (51) reported a retrospective analysis of 382 consecutive patients with severe MS in sinus rhythm who had successful balloon valvotomy and were followed for a mean of 5.6 years. Thirty-four (8.9%) patients developed AF compared with 348 (91.1%) who remained in sinus rhythm at follow-up. They compared these results with a reported series in the literature of patients with MS where AF occurred in 29% of patients with similar baseline characteristics who did not have an intervention. The baseline characteristics that were predictive of the late postvalvotomy development of AF were older age, larger left atrium, and a smaller mitral valve area at follow-up.

These findings differ from an earlier report by Krasuski and colleagues (52) of a prospective cohort of patients with MS and no history of trial arrhythmias, who showed no decrease in AF after successful versus unsuccessful balloon valvotomy. Advanced age and left atrial dimension were the best predictors of AF at follow-up, whereas procedural success at balloon valvotomy and left trial pressure reduction did not have an impact on the incidence of late AF.

Surgical Management of Mitral Valve Disease

The surgical management of mitral valve disease in the 65 to 75 age group is not much different than in younger patients, except that older patients have more comorbidity, which increases the mortality and morbidity of surgery. Over age 75 years, there is a marked increase in surgical mortality and morbidity related to limited cardiac, renal, and pulmonary reserves. Since prolongation of life is not as likely in this age group, other therapeutic goals must justify surgery, such as improvement in quality of life (QOL) and return to independent lifestyle. Surgery in an unacceptably symptomatic patient should not be denied on the basis of age alone, and a patient who is symptomatically doing well should not be subjected to surgery with its higher mortality and morbidity.

MS

Open commissurotomy should be considered when the valve is flexible enough to open when the commissures are released, there is minimal MR, but the subvalvular apparatus is obstructive, when there is thrombus in the left atrium, especially in the body of the left atrium, that remains after two to three months of anticoagulation, which would make
Mitral Valve Disease in the Elderly

Table 3 Mitral Commissurotomy Vs. Mitral Valve Replacement

<table>
<thead>
<tr>
<th></th>
<th>Commissurotomy</th>
<th>Valve replacement</th>
</tr>
</thead>
<tbody>
<tr>
<td>10-yr survival rate (percent)</td>
<td>98.7 ± 1%</td>
<td>93.7 ± 3%</td>
</tr>
<tr>
<td>Freedom from reop (percent)</td>
<td>88.1 ± 2%</td>
<td>97.7 ± 1%</td>
</tr>
<tr>
<td>Freedom from emboli (percent)</td>
<td>93.7 ± 2%</td>
<td>83.9 ± 7%</td>
</tr>
<tr>
<td>Freedom from hemorrhage (percent)</td>
<td>99.3 ± 0.5%</td>
<td>98.4 ± 1%</td>
</tr>
</tbody>
</table>

Source: From Ref. 53.

balloon valvotomy hazardous (35). At surgery, the subvalvular structures can be separated, the commissures opened, and the valve preserved. If not, the valve can be replaced.

Cotrufo and colleagues (53) reported 540 consecutive MS patients, 340 with mitral commissurotomy and 240 with a bileaflet valve replacement. The majority of patients were less than 65 years of age at the time of surgery. Hospital mortality was 2% in each group (Table 3). With a 15-year follow-up, late mortality was lower in the open commissurotomy group (1%) than in the valve replacement group (3%). With the exception of a greater incidence of reoperation, long-term results were better in the open commissurotomy group. This observation is consistent with many other studies that found that mitral valve repair is preferable to replacement (54,55).

With balloon valvotomy available for most patients with MS, the incidence of open commissurotomy has decreased. With the operative technique of preserving the papillary muscle-chordal apparatus in mitral valve replacement, the long-term outcome has approached that of valve commissurotomy. Ismeno and colleagues (56) report 313 patients with isolated MS who received either balloon valvulotomy, open commissurotomy, or valve replacement. (Table 4). There was no difference in operative mortality or seven-year actuarial survival. Freedom from reoperation was significantly better in those with mitral valve replacement and the mean functional class at the end of the follow-up period was lowest in those with open commissurotomy. At present, conservative techniques are the best, especially in the elderly. With the latest operative techniques, the late outcome after mitral valve replacement has markedly improved.

MR

With the present techniques, most patients with MR (except those with extensive loss of flexible leaflet tissue) can have the valve repaired successfully, but the selection of patients and the expertise of the surgeon are critical factors for success (55). MR due to

Table 4 Outcome of MS Intervention

<table>
<thead>
<tr>
<th></th>
<th>BV</th>
<th>OC</th>
<th>VR</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number</td>
<td>111</td>
<td>82</td>
<td>120</td>
</tr>
<tr>
<td>7-yr survival (%)</td>
<td>95.4</td>
<td>95.1</td>
<td>92.8 (p = NS)</td>
</tr>
<tr>
<td>Freedom from emboli (%)</td>
<td>95.8</td>
<td>98.8</td>
<td>92.5 (p &gt; 0.05)</td>
</tr>
<tr>
<td>Freedom from reop (%)</td>
<td>84.4</td>
<td>96.4</td>
<td>97.7 (p &gt; 0.05)</td>
</tr>
<tr>
<td>NYHA class at follow-up</td>
<td>1.39</td>
<td>1.14</td>
<td>1.41 (p = 0.001)</td>
</tr>
</tbody>
</table>

Abbreviations: BV, balloon valvulotomy; OC, open commissurotomy; VR, valve replacement; NS, not significant.

Source: from Ref. 56.
rheumatic heart disease is characterized by fibrosis and retraction of the leaflet edges as well as chordal shortening and fusion (57). Repair is least successful in this group and selection of the proper patients for repair is essential (57). Most MR in the elderly is caused by myxomatous redundant leaflets, and these are ideal candidates for valve repair. With ischemic MR or a dilated left ventricle and left ventricular OS, annuloplasty, with or without an annular ring, is frequently sufficient to create a competent valve (58). However, restricted leaflet motion can make the repair less predictable.

Contraindications for repair are loss of leaflet area, extreme leaflet thickening, or calcification of leaflets or commissures (57). Some surgeons have suggested that calcification of the annulus or leaflets does not preclude successful valve repair (59). Grossi and colleagues (60) reported the results of mitral valve repair in 558 patients. Debridement of calcification in annulus and/or leaflets was necessary in 64 (11.5%) patients. Freedom from reoperation at 10 years was 88.1% for debrided patients and 82.6% for those not needing debridement. When good annulus and leaflet mobility can be achieved in calcified valves, calcium debridement allows durable valve repair.

Patients with a small mitral annulus or multiple leaflet defects have a small probability of being successfully repaired. Patients with small left ventricular cavities, most often seen in elderly women, have a high incidence of postoperative systolic anterior motion and left ventricular outflow tract obstruction (55). Patients with mitral valve prolapse involving the posterior leaflet have the most success with repair. However, recently, there have been reports of successful repair of anterior leaflet prolapse (61,62). For the best results, patient needs a careful evaluation by TEE and an experienced surgeon.

Because the expected lifespan after surgery is shorter for the elderly patient at the time of surgery, there is an advantage of bioprosthetic valves over mechanical valves in older patients since anticoagulation is not necessary in the absence of AF. The frequency of AF in elderly patients with moderate-to-severe chronic MR lessens the advantage because these patients require anticoagulants to prevent systemic emboli (35). There is evidence that valve degeneration occurs much more slowly in the elderly than in younger patients. In one study, the rate of primary structural deterioration in patients over age 65 years was 0.95% per patient-year (63). For this reason, in patients over 65 years of age, the preferred valve is a bioprosthetic one.

Dalrymple-Hay and colleagues (54) reported 329 patients with MR due to myxomatous degeneration, mean age 65.5 years with valve repair in 169 and valve replacement in 160 patients. Operative mortality occurred in four (1.2%), all in those with valve replacement. Actuarial survival at 1, 5, and 10 years was 94 ± 1.4%, 77 ± 2.9%, and 41 ± 5.8%, with survival in patients with repair significantly better (p < 0.05) than with valve replacement. Reoperation was required in 10 (6%) of those with valve repair and in 13 (8%) of those with valve replacement. Increased age, worse left ventricular function, the type of operation (repair vs. replacement), and left ventricular size all were significantly associated with poorer survival.

Gogbashian and colleagues (64) reported a 10-year experience of mitral valve repair versus replacement in 292 patients aged 70 years and over for MR due to mitral valve prolapse, including patients with concomitant revascularization. Comparing repair to replacement, in-hospital mortality was higher (0.7% vs. 13.9%), length of hospital stay longer (8.7 vs. 9.6 days), and with greater five-year survival (81% vs. 63%). The 10-year freedom from valve reoperation in the patients with repair was 93.9% and for repair plus coronary bypass surgery 98.2%. They concluded that the preferred option for elderly patients was mitral valve repair.
Lee and colleagues (65) reported 614 patients with valve surgery for severe MR, 190 aged 70 and older and 424 under age 70. In the older patients, there was significantly more myxomatous disease, coronary disease, worse left ventricular function, and worse NYHA class III to IV symptoms. Operative mortality in both young and old patients was low (3.5% vs. 3.7%). In the older patients, seven-year survival was lower than in the young (49 ± 6% vs. 72 ± 3%) as were overt heart failure (74 ± 3% vs. 44 ± 7%) and complication-related deaths (78 ± 3% vs. 57 ± 7%). However, both young and old patients who were NYHA class I with an EF greater than 40% had the same freedom from complication-related death (93 ± 3% in the younger vs. 90 ± 7% in the elderly). These findings support the approach to early surgery once symptoms occur and before the EF begins to fall, especially if valve repair is possible.

There is good evidence that valve repair or replacement for MR improves the QOL. Goldsmith and colleagues (66), in a prospective study of 61 consecutive patients with severe MR, mean age 64 ± 12 years, who had mitral valve repair (40) or replacement (21) obtained QOL scores using the short form 36-questionnaire before and three months after surgery. There was significant improvement in seven out of eight QOL parameters in those with repair and in three out of eight in those with valve replacement. Patients with EF greater than or equal to 50% improved in seven out of eight parameters. Those with impaired function or end-systolic dimensions of greater than or equal to 45 mm showed no improvement in any of the parameters. These findings support the importance of early surgery before a decline in left ventricular function.

Grossi and colleagues (67) studied 278 patients with mitral valve repair aged 70 and older (mean age 75.2 years). Concomitant procedures were done in 72.3%, with over half having coronary revascularization. Mortality was lower in those with isolated mitral valve repair than in those with concomitant revascularization (6.5% vs. 17%). With an additional valve procedure, the mortality was 13.2%. Long-term survival was excellent with freedom from cardiac death in 100% of those with isolated mitral valve repair, lower in those with a concomitant procedure (79.7%; \( p = 0.006 \)), and freedom from reoperation in 91.2% patients.

Surgery for MR in octogenarians is usually reserved for patients who are very symptomatic despite optimal medical management. There is evidence of recent improvement in the results of surgery for MR in these elderly patients. DeTaint and colleagues (68) reported the results of surgery for MR performed from 1980 to 1995 in patients greater than or equal to 75 years of age (group 1), 65–75 (group 2), and less than 65 (group 3). Preoperatively, Group 1 patients had a higher prevalence of Functional Class III–IV symptoms, more AF and coronary disease, increased creatinine, and higher comorbidity index. The temporal trend of operative mortality showed a decrease in each age group from 27% to 5% in Group 1, 21% to 4% in Group 2, and 7% to 2% in Group 3. Over time, the feasibility of valve repair also increased, in all Groups from 30% to 54%, and in those with degenerative MR (mitral valve prolapse) from 31% to 93%.

Multivariate analysis of relative survival showed no difference in restoration of life expectancy compared with younger patients (Table 5). Recent improvements in surgery have benefited elderly patients who should be carefully considered for surgery before refractory heart failure is present.

Present guidelines (35) recommend that surgery may be postponed safely in asymptomatic patients with severe MR, even if repair is possible, until the patient develops symptoms or AF, evidence of left ventricular dysfunction with EF falling below 60%, or LVESD increases to 45 mm, or pulmonary hypertension becomes greater than 50 mmHg at rest or greater than 60 mmHg with exercise. Rosenheek and colleagues (34)
reported 132 such patients 55 ± 15 years of age with severe MR due to mitral valve prolapse or flail leaflet. They underwent serial clinical and echocardiographic monitoring and were followed prospectively for 62 ± 26 months. They were referred for surgery for the above criteria. Only 30% of patients needed surgery by five years and fewer than half by eight years. Symptoms were the commonest indication for surgery. There was no operative mortality and the postoperative outcome was good with regards to survival, symptomatic status and late left ventricular function.

Valve replacement is performed in more elderly patients for aortic valve than for mitral valve disease, most often calcific aortic stenosis, and operative mortality is lower than with mitral valve replacement (69,70). Helft and colleagues (63) reported 110 patients, 65 and older (mean 73.4 years), with bioprosthetic valve replacement, 71 with aortic, 32 with mitral, and seven with both. Follow-up was 8.5 years. At five years the actuarial survival was 79.6% and at 10 years 62.4%. Of the 44 patients who died, over half (52.3%) died from non-valve–related causes. Reoperation was needed in 13 patients (11.8%), 10 for structural deterioration, with one death (7.7%). Anticoagulation for AF was needed in 26%, with 6.4% developing severe bleeding (2.9% per patient-year). Similar results have been reported in octogenarians (71–73). In examining the reasons for a higher mortality in octogenarians with MR surgery compared to aortic valve surgery, it is probable that the higher mortality is related more to the patients’ preoperative clinical state and comorbidities than to the type of surgery (71).

With MR due to ischemia, operative and late mortality is higher than with MR due to myxomatous degeneration (30). Operative mortality is also higher when the EF is 30% or lower. Hausmann and colleagues (30) reported 337 patients with ischemic MR and mitral valve repair or replacement (Table 6). The goal of surgery in patients with ischemic MR is to reduce the MR to no more than grade 1.

### Table 5: Long-Term Survival After Surgery For MR

<table>
<thead>
<tr>
<th>Gr</th>
<th>Number</th>
<th>5-yr survival</th>
<th>Rate of observed/expected survival (for age)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>284</td>
<td>57 ± 3%</td>
<td>83%</td>
</tr>
<tr>
<td>2</td>
<td>504</td>
<td>73 ± 2%</td>
<td>85%</td>
</tr>
<tr>
<td>3</td>
<td>556</td>
<td>85 ± 2% (p &lt; 0.001)</td>
<td>88% (p = NS)</td>
</tr>
</tbody>
</table>

*Abbreviations: MR, mitral regurgitation; NS, not significant.*

*Source: From Ref 68.*

### Table 6: Surgery for Ischemic MR

<table>
<thead>
<tr>
<th>Type of operation</th>
<th>n</th>
<th>Op mort</th>
<th>10–30%</th>
<th>&gt;30%</th>
<th>2 yr</th>
<th>5 yr</th>
<th>7 yr</th>
</tr>
</thead>
<tbody>
<tr>
<td>Valve repair</td>
<td>140</td>
<td>12.1%</td>
<td>33.3%</td>
<td>8.4%</td>
<td>75.4%</td>
<td>66.8%</td>
<td>61.7%</td>
</tr>
<tr>
<td>Valve replace</td>
<td>197</td>
<td>14.2%</td>
<td>30.3%</td>
<td>11.0%</td>
<td>78.6%</td>
<td>73.4%</td>
<td>67.2%</td>
</tr>
<tr>
<td>When MR reduced to grade 0–1 patient survival best</td>
<td>160</td>
<td>14.2%</td>
<td>30.3%</td>
<td>11.0%</td>
<td>78.6%</td>
<td>73.4%</td>
<td>67.2%</td>
</tr>
</tbody>
</table>

*Abbreviations: Op mort, Operative mortality; EF, ejection fraction.*

*Source: From Ref. 30.*
Figure 16.6 Two-dimensional echocardiographic image from an apical four-chamber view in an elderly patient with severe aortic insufficiency, showing a large diastolic aliasing color Doppler jet in the left ventricular outflow tract. Abbreviations: AI, aortic insufficiency; LV, left ventricular cavity; MV, mitral valve leaflets; LA, left atrium; RA, right atrium.
Figure 16.7  Continuous-wave Doppler recording of the velocity profile across the aortic valve in the same patient shown in Figure 16.6. A holosystolic decrescendo high-velocity profile is recorded from the left ventricular outflow tract, characteristic of aortic insufficiency. *Abbreviation:* AI, aortic insufficiency.
Figure 17.6  Color Doppler echocardiographic findings in a patient with mitral annular calcium and severe MR. *Abbreviations:* LA, left atrium; RA, right atrium; RV, right ventricle; LV, left ventricle; MR, mitral regurgitation.
Figure 19.11 Color Doppler flow display from a patient with obstructive hypertrophic cardiomyopathy shows turbulent flow in the LVOT and mild mitral regurgitation (MR). Abbreviation: LVOT, left ventricular outflow tract.
A frequent problem with ischemia and 1 to 3+ MR is whether to simply revascularize the patient or also make the mitral valve more competent, usually with an annuloplasty. Grossi and colleagues (74) in evaluating the impact of moderate MR in patients undergoing isolated coronary surgery followed 2242 consecutive patients with no to moderate MR. They found that, independent of ventricular function, that mild to moderate MR is associated with significantly decreased survival.

Tolis and colleagues (75) had 49 patients, mean age 66.3 years with advanced ischemic heart disease, 1 to 3+ MR (62% had 2–3+ MR), and an EF of 10% to 30% (mean 22.4%). In-hospital mortality was 2% and the mean degree of MR went from 1.73 down to 0.54 (p < 0.05). The NYHA class decreased from 3.3 to 1.8 (p < .05) and the EF rose from 22% to 31.5% (p < 0.05). The one-, three-, and five-year survivals were 88%, 65%, and 50%. They concluded that in such patients revascularization was sufficient and that improvement in MR and EF occur from improved left ventricular function and size after revascularization.

Aklog and colleagues (58) reported 136 patients, mean age 70.5 years with ischemic heart disease and more severe 3+ MR with a mean EF of 38.1%. Operative mortality was 2.9%. They found the intraoperative TEE underestimated the degree of MR and the postoperative TTE revealed that 40% of the patients still had 3+ MR, 51% improved to 2+ MR, and only 9% had 0 to 1+ MR. They concluded that ischemic MR required more than just revascularization, usually concomitant annuloplasty. Campwala and colleagues (76) reported the fate of MR following surgical revascularization in 523 patients, 92 of whom had 3 to 4+ MR on preoperative echocardiogram. Post surgery, residual 3 to 4+ MR was present in 43 (47%) patients and was associated with a trend to increased mortality (p = 0.3) over a mean follow-up of 3.9 years. Other studies have reported benefit in terms of symptoms and improved survival in patients with severe left ventricular dysfunction and MR (77), not only due to coronary artery disease but also in patients with cardiomyopathy and chronic valvular regurgitation (78,79).

MITRAL ANNULAR CALCIFICATION

Mitral annular calcium (MAC) is a chronic degenerative process that is common in elderly persons, especially women. The amount of calcium may vary from a few spicules to a large mass behind the posterior cusp, often extending to form a ridge or ring encircling the mitral leaflets, occasionally lifting the leaflets toward the left atrium. Sphincter function loss of the mitral annulus and mechanical stretching of the mitral leaflets can cause improper coaptation of the leaflets during systole, resulting in MR (62). Although the calcific mass may immobilize the mitral valve, actual calcification of the leaflets is rare. In persons with severe MAC, the calcification may extend inward to involve the underside of the leaflets. MS may result from severe calcific deposits within the mitral annulus protruding into the orifice (1). Calcific deposits may extend from the mitral annulus into the membranous portions of the ventricular septum, involving the conduction system and causing rhythm and conduction disturbances (80). Although the annular calcium is covered with a layer of endothelium, ulceration of this lining can expose the underlying calcific deposits, which may serve as a nidus for platelet-fibrin aggregation and subsequent thromboembolic episodes (81,82). In patients with endocarditis associated with MAC, the avascular nature of the mitral anulus predisposes to perianular and myocardial abscesses (83,84).
Prevalence

MAC is a degenerative process that increases with age and occurs more frequently in women than in men (82,85). In a prospective study of 1797 unselected elderly persons in a long-term health-care facility, mean age 81 ± 8 years (range 60 to 103 years), with technically adequate M-mode and two-dimensional echocardiograms of the mitral valve, MAC was present in 665 of 1243 women (53%) and in 194 of 554 men (35%) (86). Table 7 shows the prevalence of MAC with increasing age in elderly men and elderly women (87).

Predisposing Factors

Because calcific deposits in the mitral annulus, in the aortic valve cusps, and in the epicardial coronary arteries are commonly associated in elderly persons and have similar predisposing factors, Roberts (88) suggested that MAC and aortic cuspal calcium are a form of atherosclerosis. MAC and aortic cuspal calcium may coexist (80,82,85,88–90). Breakdown of lipid deposits on the ventricular surface of the posterior mitral leaflet or below the mitral annulus and on the aortic surfaces of the aortic valve cusps is probably responsible for the calcification (80). Increased left ventricular systolic pressure due to aortic valve stenosis increases stress on the mitral apparatus and may accelerate development of MAC (80,82,91). Tricuspid annular calcium and MAC may also coexist and have similar predisposing factors (92).

Systemic hypertension increases with age and predisposes to MAC (80,82,83,85,86). Persons with diabetes mellitus also have a higher prevalence of MAC than nondiabetic persons (80,89,90). MAC occurs in the teens with serum total cholesterol levels greater than 500 mg/dL (93). Waller and Roberts (94) suggested that hypercholesterolemia predisposes to MAC. The prevalence of hypercholesterolemia with serum total cholesterol greater than 200 mg/dL was higher in elderly persons with MAC than in elderly persons without MAC (90). Roberts (88) also stated that MAC is rare in older persons residing in areas of the world where serum total cholesterol levels are less than 150 mg/dL. However, Nair and colleagues (89) found no significant difference in mean serum total cholesterol levels between persons younger than 60 years with MAC and a control group.

Yetkin and colleagues (95) reported 484 consecutive patients, mean age 60 ± 10, undergoing coronary arteriography for suspected coronary artery disease. Twenty percent of them had MAC. There were no statistically significant differences between those with

<table>
<thead>
<tr>
<th>Age (yr)</th>
<th>Men</th>
<th>Women</th>
</tr>
</thead>
<tbody>
<tr>
<td>62–70</td>
<td>4/22 18</td>
<td>7/35 20</td>
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<tr>
<td>71–80</td>
<td>13/42 31</td>
<td>40/116 34</td>
</tr>
<tr>
<td>81–90</td>
<td>44/75 59</td>
<td>146/226 65</td>
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<td>91–100</td>
<td>19/22 86</td>
<td>56/63 89</td>
</tr>
<tr>
<td>101–103</td>
<td>—</td>
<td>3/3 100</td>
</tr>
</tbody>
</table>

Abbreviation: MAC, Mitral Annular Calcium.
Source: Adapted from Ref. 87.
and without MAC with respect to body mass index, diabetes mellitus, hypercholesterolemia, or the presence of coronary artery disease.

Roberts and Waller (96) found that chronic hypercalcemia predisposes to MAC. Patients undergoing dialysis for chronic renal insufficiency have an increased prevalence of MAC (96,97). MAC has also been found to be a marker of left ventricular dilatation and decreased left ventricular systolic function in patients with end-stage renal disease on peritoneal dialysis (98). Fox and colleagues (99) studying 3047 participants in the Framingham study of patients with chronic kidney disease, defined by a glomerular filtration rate less than 60 ml/min/1.73 m², found that the odds of having MAC was increased by 60% in those with chronic kidney disease. Nair and colleagues (89) demonstrated a similar mean serum calcium, a higher mean serum phosphorus, and a higher mean product of serum calcium and phosphorus in patients younger than 60 years with MAC than in a control group. However, Aronow and colleagues (90) observed no significant difference in mean serum calcium, serum phosphorus, or product of serum calcium and phosphorus between elderly persons with and without MAC. By accelerating the rate of rise of left ventricular systolic pressure, hypertrophic cardiomyopathy predisposes to MAC (80). Kronzon and Glassman (100) diagnosed MAC in 12 of 18 patients (67%) older than 55 years with hypertrophic cardiomyopathy and in 4 of 28 patients (14%) younger than 55 years with hypertrophic cardiomyopathy. Motamed and Roberts (101) demonstrated MAC in 30 of 100 autopsy patients (30%) with hypertrophic cardiomyopathy older than 40 years and in none of 100 autopsy patients (0%) younger than 40 years with hypertrophic cardiomyopathy. Aronow and Kronzon (102) diagnosed MAC in 13 of 17 older persons (76%) with hypertrophic cardiomyopathy and in 176 of 362 older persons (49%) without hypertrophic cardiomyopathy.

Elderly men and women with MAC have a higher prevalence of coronary artery disease (103–105), of peripheral arterial disease (105,106), of extracranial carotid arterial disease (ECAD) (105,107,108), and of aortic atherosclerotic disease (105) than elderly men and women without MAC. MAC has also been shown to be associated with thoracic aorta calcium in patients with systemic hypertension (109).

Diagnosis

Calcific deposits in the mitral annulus are J, C, U, or O-shaped and are visualized in the posterior third of the heart shadow (82,110,111). MAC may be diagnosed by chest X-ray films or by fluoroscopy (111). However, the procedures of choice for diagnosing MAC are M-mode and two-dimensional echocardiography.

Posterior MAC (Fig. 1) is diagnosed by M-mode echocardiography when a band of dense echoes is recorded anterior to the left ventricular posterior wall and moving parallel with it (112). These echoes end at the atrioventricular junction and merge with the left ventricular posterior wall on echocardiographic sweep from the aortic root to the left ventricular apex.

Anterior MAC (Fig. 1) is diagnosed by M-mode echocardiography when a continuous band of dense echoes is observed at the level of the anterior mitral leaflet in both systole and diastole (112). These echoes are contiguous with the posterior wall of the aortic root. Calcification may extend from the mitral annulus throughout the base of the heart and into the mitral and aortic valves.

Figures 2 and 3 are two-dimensional echocardiograms showing increased echogenicity and brightness of the mitral annulus characteristic of MAC. Using multiple echocardiographic views, MAC may be classified as mild, moderate, or severe (113). The echo densities in mild MAC involve less than one-third of the annular circumference.
(<3 mm in width) and are usually restricted to the angle between the posterior leaflet of the mitral valve and the left ventricular posterior wall. The echo densities in moderate MAC involve less than two-thirds of the annular circumference (3–5 mm in width). The echo densities in severe MAC involve more than two-thirds of the annular circumference.
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Figure 3 Two-dimensional echocardiogram four-chamber view of a patient with MAC. Abbreviations: LA, left atrium; RA, right atrium; RV, right ventricle; LV, left ventricle; AML, anterior mitral leaflet; PML, posterior mitral leaflet; MAC, mitral annular calcium.

(>5 mm in width), usually extending beneath the entire posterior mitral leaflet with or without making a complete circle.

In a blinded prospective study, MAC was diagnosed by M-mode and two-dimensional echocardiography in 55% of 604 unselected elderly patients in a long-term healthcare facility (111). The diagnosis of MAC by chest X-ray films using a lateral chest X-ray in addition to the posterior-anterior or anterior posterior chest X-ray had a sensitivity of 12%, a specificity of 99%, a positive predictive value of 95%, and a negative predictive value of 47%. Patients with radiographic MAC were more likely than patients without radiographic MAC to have a more severe form of the disease, with significant MR, functional MS, or conduction defects. However, patients with echocardiographically severe MAC and significant MR, functional MS, or conduction defects may have no evidence of MAC on chest X-ray films. Figure 4 shows C-shaped calcification of the mitral annulus. Figure 5 illustrates J-shaped calcification of the mitral annulus.

**Chamber Size**

Patients with MAC have a higher prevalence of left atrial enlargement (80,83,85,87,89,113) and left ventricular enlargement (85,89,113) than patients without MAC. In a prospective study of 976 elderly patients (526 with MAC and 450 without MAC), left atrial enlargement was 2.4 times more prevalent in patients with MAC than in the group without MAC (83).

**AF**

Patients with MAC also have a higher prevalence of AF than patients without MAC (82,83,85,87,113,114). Table 8 shows that the prevalence of AF was increased 12, 5, and 2.8 times in patients with MAC than in patients without MAC (85,89,114).
Conduction Defects

Because of the close proximity of the mitral annulus to the atrioventricular node and the bundle of His, patients with MAC have a higher prevalence of conduction defects, such as sinoatrial disease, atrioventricular block, bundle branch block, left anterior fascicular block, and intraventricular conduction defect, than patients without MAC (81,82,91,113). The calcific deposits may also extend into the membranous portions of the interventricular septum involving the conduction system, or may even extend to the left atrium, interrupting interatrial and intra-atrial conduction. In addition, MAC may be associated with a sclerodegenerative process in the conduction system. Nair et al. (113) showed in

Figure 4  Posterior-anterior chest X-ray in a patient with C-shaped calcification of the mitral annulus (arrows).
their prospective study that patients with MAC had a higher incidence of permanent pacemaker implantation because of both atrioventricular block and sinoatrial disease than patients without MAC.

**MR**

MAC is thought to generate systolic murmurs by the sphincter action loss of the annulus and the mechanical stretching of the mitral leaflets causing MR and from vibration of the
calcified ring or vortex formation around the annulus. Table 9 shows that the prevalence of apical systolic murmurs of MR in patients with MAC ranged from 12% to 100% in different studies (82,85,89,115–118). Table 10 states the prevalence of MR diagnosed by Doppler echocardiography in patients with MAC (114,118–120). The prevalence of MR associated with MAC ranged from 54% to 97% in the Doppler echocardiographic studies (118–120). Figure 6 illustrates severe MR due to MAC diagnosed by color Doppler echocardiography.

### Table 8

<table>
<thead>
<tr>
<th></th>
<th>MAC</th>
<th></th>
<th>No MAC</th>
<th></th>
<th>Relative risk</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n</td>
<td>%</td>
<td>n</td>
<td>%</td>
<td></td>
</tr>
<tr>
<td>Framingham Study (85)</td>
<td>20/162</td>
<td>12</td>
<td>53/5532</td>
<td>1</td>
<td>12</td>
</tr>
<tr>
<td>Patients younger than 61 yr (89)</td>
<td>11/107</td>
<td>10</td>
<td>2/107</td>
<td>2</td>
<td>5</td>
</tr>
<tr>
<td>Patients older than 60 yr (mean age 81 + 8 yr) (114)</td>
<td>225/1028</td>
<td>22</td>
<td>85/1120</td>
<td>8</td>
<td>2.8</td>
</tr>
</tbody>
</table>

*Abbreviation: MAC, mitral annular calcium.*

### Table 9

<table>
<thead>
<tr>
<th>Study</th>
<th>MR</th>
<th>%</th>
<th>Relative risk</th>
</tr>
</thead>
<tbody>
<tr>
<td>Korn et al. (115)</td>
<td>14/14</td>
<td>100</td>
<td></td>
</tr>
<tr>
<td>Schott et al. (116)</td>
<td>10/14</td>
<td>71a</td>
<td></td>
</tr>
<tr>
<td>Fulkerson et al. (82)</td>
<td>72/80</td>
<td>90</td>
<td></td>
</tr>
<tr>
<td>Savage et al. (85)</td>
<td>26/132</td>
<td>12</td>
<td></td>
</tr>
<tr>
<td>Nair et al. (89)</td>
<td>17/104</td>
<td>16</td>
<td></td>
</tr>
<tr>
<td>Aronow et al. (117)</td>
<td>129/293</td>
<td>44</td>
<td></td>
</tr>
<tr>
<td>Aronow et al. (118)</td>
<td>43/100</td>
<td>43</td>
<td></td>
</tr>
</tbody>
</table>

*aMAC due to noninflammatory calcific disease.*

*Abbreviations: MR, mitral regurgitation; MAC, mitral annular calcium.*

### Table 10

<table>
<thead>
<tr>
<th>Study</th>
<th>MR</th>
<th>%</th>
<th>Moderate-to-severe MR</th>
<th>N</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Labovitz et al. (120)</td>
<td>28/51</td>
<td>55</td>
<td>17/51</td>
<td>33</td>
<td></td>
</tr>
<tr>
<td>Aronow et al. (118)</td>
<td>54/100</td>
<td>54</td>
<td>18/100</td>
<td>18</td>
<td></td>
</tr>
<tr>
<td>Kaul et al. (119)</td>
<td>28/29</td>
<td>97a</td>
<td>——</td>
<td>——</td>
<td></td>
</tr>
<tr>
<td>Aronow et al. (114)</td>
<td>——</td>
<td>——</td>
<td>24/1028</td>
<td>22</td>
<td></td>
</tr>
</tbody>
</table>

*aSevere MR in 2 of 29 patients (7%).*  
*Abbreviations: MR, mitral regurgitation; MAC, mitral annular calcium.*
The greater the severity of MAC, the greater is the severity of MR associated with MAC. Moderate-to-severe MR was diagnosed by Doppler echocardiography in 33% of 51 patients with MAC by Labovitz and colleagues (120) and in 22% of 1028 patients with MAC by Aronow and colleagues (114). Kaul and colleagues (119) diagnosed severe MR in 7% of their 29 patients with MAC, and concluded that MR in patients with MAC is caused by a reduced sphincteric action of the mitral annulus, with MAC preventing the posterior annulus from contracting and assuming a flatter shape during systole.

MS

An apical diastolic murmur may be heard in patients with MAC as a result of turbulent flow across the calcified and narrowed annulus (annular stenosis). Table 11 shows that the prevalence of apical diastolic murmurs of MS in patients with MAC ranged from 0% to 25% in different studies (85,113–118,120,121). Table 11 also indicates that MS associated with MAC was diagnosed by Doppler echocardiography in 8% of 51 patients by Labovitz and colleagues (120), in 6% of 100 patients by Aronow and Kronzon (118), and in 8% of 1028 patients by Aronow et al. (114). Figure 7 illustrates MS due to MAC diagnosed by Doppler echocardiography.

The reduction of mitral valve orifice in patients with MAC is due to the annular calcium and to decreased mitral excursion and mobility secondary to calcium at the base of the leaflets (118). The commissures are fused in rheumatic MS but are not fused in MS associated with MAC. The mitral leaflet margins in MAC may be thin and mobile, and the posterior mitral leaflet may move normally during diastole. However, Doppler echocardiographic recordings show increased transvalvular flow velocity and prolonged
Figure 7  Continuous-wave Doppler tracing across a stenotic mitral valve orifice due to mitral annular calcium. Peak diastolic gradient = 12 mmHg. Pressure halftime = 200 milliseconds. Mitral valve area = 1.1 cm\(^2\).

**Table 11** Prevalence of Apical Diastolic Murmurs of MS and of MS in Patients with MAC

<table>
<thead>
<tr>
<th></th>
<th>Prevalence of MS murmur</th>
<th>Prevalence of MS by Doppler echocardiography</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n</td>
<td>%</td>
</tr>
<tr>
<td>Simon and Liu (121)</td>
<td>5/59 8</td>
<td>—</td>
</tr>
<tr>
<td>Korn et al. (115)</td>
<td>3/14 21</td>
<td>—</td>
</tr>
<tr>
<td>Schott et al. (116)</td>
<td>2/14 14(^a)</td>
<td>—</td>
</tr>
<tr>
<td>Savage et al. (85)</td>
<td>2/132 2</td>
<td>—</td>
</tr>
<tr>
<td>Nair et al. (113)</td>
<td>7/104 7</td>
<td>—</td>
</tr>
<tr>
<td>Aronow et al. (117)</td>
<td>28/293 10</td>
<td>—</td>
</tr>
<tr>
<td>Labovitz et al. (120)</td>
<td>0/51 0</td>
<td>4/51 8</td>
</tr>
<tr>
<td>Aronow et al. (118)</td>
<td>6/100 6</td>
<td>83/1028 8</td>
</tr>
<tr>
<td>Aronow et al. (114)</td>
<td>— —</td>
<td>—</td>
</tr>
</tbody>
</table>

\(^a\)MAC due to noninflammatory calcific disease.

*Abbreviations:* MS, mitral stenosis; MAC, mitral annular calcium.
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pressure halftime and, therefore, smaller mitral valve orifice in patients with MS, regardless of the etiology.

**Bacterial Endocarditis**

Bacterial endocarditis, with a high incidence of *Staphylococcus aureus* endocarditis, may complicate MAC (82,83). Patients with MAC associated with chronic renal failure are especially at increased risk for developing bacterial endocarditis (116). The calcific mass erodes the endothelium under the mitral valve, which is exposed to transient bacteremia. The avascular nature of the mitral annulus interferes with antibiotics reaching a nidus of bacteria, predisposing to perianular and myocardial abscesses and, consequently, to a poor prognosis (122). Burnside and DeSanctis (122) therefore recommended prophylactic antibiotics to prevent bacterial endocarditis in patients with MAC. Nair and colleagues (113) observed at 4.4-year mean follow-up with no significant difference in incidence of bacterial endocarditis in 99 patients younger than 61 years with MAC compared to a control group of 101 patients. However, Aronow and colleagues (83) demonstrated at 39-month mean follow-up a 3% incidence of bacterial endocarditis in 526 elderly patients with MAC and a 1% incidence of bacterial endocarditis in 450 elderly patients without MAC. On the basis of these data, prophylactic antibiotics should be used to prevent bacterial endocarditis in patients with MAC, according to American Heart Association guidelines (123).

**Cardiac Events**

In a prospective study of 107 patients (8 lost to follow-up) younger than 61 years with MAC and 107 (6 lost to follow-up) age- and sex-matched control subjects, Nair and colleagues (113) demonstrated at 4.4-year mean follow-up that patients with MAC had a higher incidence of new cardiac events than control subjects (Table 12). In a prospective study of 526 elderly patients with MAC and 450 elderly patients without MAC, Aronow and colleagues (83) found at 39-month mean follow-up that the incidence of new cardiac events (myocardial infarction, primary ventricular fibrillation, or sudden cardiac death) was also higher in elderly patients with MAC than in elderly patients without MAC (Table 12).

**Mitral Valve Replacement**

Nair and colleagues (124) reported that mitral valve replacement could be accomplished in patients with MAC with morbidity and mortality similar to that in patients without MAC. Following mitral valve replacement, subsequent morbidity and mortality during 4.4-year mean follow-up were also similar in patients with and without MAC.

**Cerebrovascular Events**

Although the increased prevalence of AF, MS, MR, left atrial enlargement, and congestive heart failure predisposes patients with MAC to thromboembolic stroke, some investigators consider MAC a marker of other vascular disease causing stroke rather the primary embolic source (125). In a retrospective study of 110 elderly patients with chronic AF, 44 (40%) had documented thromboembolic stroke (126). In this study, the prevalence of MAC was not significantly different in elderly patients with
thromboembolic stroke (80%) or without thromboembolic stroke (65%) (relative risk = 1.2). However, six prospective studies have demonstrated an increased incidence of new cerebrovascular events in patients with MAC than in patients without MAC (Tables 13–15) (83,113,114,127–129) ranging from a relative risk of 1.5 up to 5.0.

### Table 12 Incidence of New Cardiac Events in Patients With and Without MAC

<table>
<thead>
<tr>
<th>Cardiac events</th>
<th>MAC</th>
<th>No MAC</th>
<th>Relative risk</th>
</tr>
</thead>
<tbody>
<tr>
<td>Follow-up</td>
<td>n</td>
<td>%</td>
<td>n</td>
</tr>
<tr>
<td>Nair et al. (113)</td>
<td>yr</td>
<td>31/99</td>
<td>31</td>
</tr>
<tr>
<td>Total cardiac death</td>
<td>12/99</td>
<td>12</td>
<td>1/101</td>
</tr>
<tr>
<td>Sudden cardiac death</td>
<td>41/99</td>
<td>41</td>
<td>6/101</td>
</tr>
<tr>
<td>Congestive heart failure</td>
<td>9/99</td>
<td>9</td>
<td>0/101</td>
</tr>
<tr>
<td>Mitral or aortic valve replacement</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Aronow et al. (83)</td>
<td>39 mo</td>
<td>62/90</td>
<td>69</td>
</tr>
<tr>
<td>atrial fibrillation</td>
<td>157/436</td>
<td>36</td>
<td>106/409</td>
</tr>
<tr>
<td>sinus rhythm</td>
<td>219/526</td>
<td>42</td>
<td>128/450</td>
</tr>
<tr>
<td>atrial fibrillation</td>
<td>128/526</td>
<td>24</td>
<td>106/409</td>
</tr>
</tbody>
</table>

*aMyocardial infarction, primary ventricular fibrillation, or sudden cardiac death.

**Abbreviation**: MAC, mitral annular calcium.

### Table 13 Incidence of New Cerebrovascular Events in Patients With and Without MAC

<table>
<thead>
<tr>
<th>Cerebrovascular events</th>
<th>MAC</th>
<th>No MAC</th>
<th>Relative risk</th>
</tr>
</thead>
<tbody>
<tr>
<td>Follow-up</td>
<td>n</td>
<td>%</td>
<td>n</td>
</tr>
<tr>
<td>Nair et al. (113)</td>
<td>4.4 yr</td>
<td>10/99</td>
<td>10</td>
</tr>
<tr>
<td>Benjamin et al. (127) stroke</td>
<td>8 yr</td>
<td>22/160</td>
<td>14</td>
</tr>
<tr>
<td>Aronow et al. (83)</td>
<td>39 mo</td>
<td>45/90</td>
<td>50</td>
</tr>
<tr>
<td>TE stroke if:</td>
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<td></td>
<td></td>
</tr>
<tr>
<td>atrial fibrillation</td>
<td>59/436</td>
<td>14</td>
<td>38/409</td>
</tr>
<tr>
<td>sinus rhythm</td>
<td>104/526</td>
<td>20</td>
<td>52/450</td>
</tr>
<tr>
<td>All patients</td>
<td>104/526</td>
<td>20</td>
<td>52/450</td>
</tr>
<tr>
<td>Trial for Atrial Fibrillation (128) ischemia stroke</td>
<td>2.2 yr</td>
<td>10/129</td>
<td>8</td>
</tr>
<tr>
<td>Aronow et al. (129)</td>
<td>45 mo</td>
<td>52/101</td>
<td>51</td>
</tr>
<tr>
<td>TE stroke if:</td>
<td></td>
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</tr>
<tr>
<td>40–100% ECD</td>
<td>88/365</td>
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<td>47/413</td>
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<tr>
<td>0–39% ECD</td>
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<td>3/49</td>
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<td>TIA if:</td>
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<td></td>
<td></td>
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<tr>
<td>40–100% ECD</td>
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<td>3</td>
<td>3/413</td>
</tr>
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</table>

**Abbreviations**: MAC, mitral annular calcium; TE, thromboembolic; ECD, extracranial carotid arterial disease; TIA, cerebral transient ischemic attack.
Aronow and colleagues studied the incidence of new thromboembolic stroke at 44-month mean follow-up in 310 unselected elderly patients with chronic AF in a long-term health-care facility (114) (Table 14). MS and the severity of MR were diagnosed by Doppler echocardiography in this study (114). In elderly persons with chronic AF, MAC increased the incidence of new thromboembolic stroke 2.1 times if MS was associated with MAC, 1.7 times if 2–4 + MR was associated with MAC, and 1.4 times if 0–1 + MR was present.

Table 15 shows the incidence of new thromboembolic stroke at 44-month mean follow-up in 1838 unselected older persons, mean age 81 years, with sinus rhythm, in a long-term health-care facility (114). In elderly persons with sinus rhythm, MAC increased the incidence of new thromboembolic stroke 3.6 times if MS was associated with MAC, 3.1 times if 2–4 + MR was associated with MAC, and 2.7 times if 0–1 + MR was present. Using the multivariate Cox regression model, independent risk factors for new thromboembolic stroke in this study were prior stroke (risk ratio = 2.4), MAC (risk ratio = 2.6), AF (risk ratio = 3.0), and male gender (risk ratio = 1.6).

There was a higher prevalence of MAC in elderly patients with 40% to 100% ECAD (67% of 150 patients) than in elderly patients with 0% to 39% ECAD (47% of 778 patients) (129). The increased prevalence of significant ECAD contributes to a higher stroke rate. Thrombi of the mitral annulus also contribute to thromboembolic stroke in elderly patients with MAC (130,131). In addition, MAC is associated with aortic atheromatous disease (105), complex intra-aortic debris (132), and thoracic aorta calcium (109), which could contribute to thromboembolic stroke. Some patients with MAC who experienced thromboembolic events also had a mobile component that was associated with the thromboembolic events (133). There was no significant difference in the association of MAC with prior stroke between elderly whites and elderly African-Americans, between elderly whites and elderly Hispanics, and between elderly African-Americans and elderly Hispanics (134).
Kizer and colleagues (135) from the Strong Heart Study, followed 2723 American-Indians without clinical cardiovascular disease and with baseline echocardiograms for seven years. Eighty-six strokes occurred. The presence of MAC but not aortic valve sclerosis was a strong risk factor for incident stroke after extensive adjustment for other predictors.

Since patients with MAC and AF or sinus rhythm have a higher incidence of thromboembolic stroke than patients without MAC, antithrombotic therapy should be considered in patients with MAC and no contraindications to antithrombotic therapy. In the Boston Area Anticoagulation Trial for Atrial Fibrillation study, warfarin reduced the incidence of thrombembolic stroke in patients with MAC by about 90% (136,137).

Until data from prospective, randomized studies evaluating the efficacy and risk of antithrombotic therapy in patients with MAC are available, patients with MAC associated with either AF, MS, or moderate-to-severe MR should be considered for treatment with warfarin if they have no contraindications to anticoagulant therapy. The international normalised ratio should be maintained between 2.0 and 3.0. The efficacy of antiplatelet therapy in patients with MAC is unknown.

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Infective Endocarditis in the Elderly

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Infective endocarditis (IE) is a disease with variable manifestations. In the pre–antibiotic era, endocarditis predominately occurred in the third and fourth decades of life (1), but numerous publications have now provided an increasing awareness of the growing proportion of older individuals afflicted with this disease.

William Osler provided the first comprehensive account of IE in the English literature (2). IE is generally thought to result from infection of platelet fibrin deposits on the endocardial surface (3,4) of previously damaged heart valves; however, it is now recognized that certain organisms may infect normal heart valves. The clinical manifestations of IE are many and have been previously reviewed. This chapter focuses on selected aspects of IE in older adults.

The annual incidence of infective endocarditis worldwide in 1982 was estimated to be 60 cases per million population (6), with the majority of cases occurring in males (5). However, with the aging of the population, the epidemiology of IE is evolving.

In the past, the most common predisposing factor for infection of the endocardium was rheumatic heart disease, which accounted for 25% to 60% of the cases (5). Other predisposing factors included congenital heart disease (10–20% of the cases), mitral valve prolapse, prosthetic heart valves, and degenerative processes occurring on the valves. Streptococcus viridans (S. viridans), other strains of streptococci, and staphylococci accounted for the majority of cases of bacterial endocarditis (7) in all age groups (8).

According to King and Harkness (5), IE can induce clinical manifestations in four ways: (i) constant bacteremia; (ii) local invasion; (iii) peripheral embolization; and (iv) circulating immune complexes. These mechanisms lead to the classic signs and symptoms associated with endocarditis, including changing murmurs, skin manifestations, embolic episodes, and splenomegaly.

In 1965, Rabinovich et al. (9) reviewed 327 cases of bacterial endocarditis occurring over a 40-year period at the University of Iowa Hospitals. They confirmed the male predominance (65% of the cases) of the disease and that rheumatic heart disease was the major predisposing factor, accounting for 68.2% of all the cases. Congenital heart disease accounted for 13.1% of the cases, but in 16.3% no identifiable heart disease was found. α-Hemolytic streptococci accounted for 61.4% of the cases. Fever was present in every case, skin manifestations (petechiae) in 48% of the cases, clubbing in only 15%, and
splenomegaly in 43%. Anemia was present in 78% of the patients and hematuria in 28%.
Complications included embolic episodes in 55 of the 337 individuals (16.3%) and congestive heart failure in 25 (7.4%). Among patients presenting after 1950, the early mortality rate was 30%, and the authors significantly noted that “age by itself did not seem to have any effect on the fatality rate.”

A year later, Lerner and Weinstein (10) published one of the best-known endocarditis series in the antibiotic era. They described 100 patients seen at the New England Medical Center in Boston from 1956 to 1964. These authors clearly documented the rising age of patients with endocarditis that occurred after the studies of Kelson and White (1), noting that 60% of their cases were older than 50 years. Over half (56%) of the patients were infected with streptococci (27% S. viridans), while in 23% of the cases staphylococci were the etiologic agents [20% S. aureus]. Rheumatic heart disease was the most common antecedent cardiac disorder (40%), followed by congenital heart disease (10%) and arteriosclerotic disease (3%). In 39% of cases, no predisposing cardiac disorder was identified, and the authors emphasized that many elderly patients with IE had no knowledge of antecedent cardiac disease. In this series, 97% of the patients were febrile, 85% had a heart murmur, 29% had petechiae, 44% had splenomegaly, and 30% had at least one major embolic event. Anemia was present in 50% of the cases, hematuria in 26%, and an elevated erythrocyte sedimentation rate in 90%. Age had little effect on the mortality rate until the eighth decade of life; of eight patients aged 70 years or older, seven succumbed to illness.

In 1971, Cherubin and Neu (11) reported a 30-year experience with endocarditis at Presbyterian Hospital in New York City. They reviewed the records of 656 cases of IE seen between 1938 and 1967. They also appreciated the increasing mean age of the patients, from 31 years in 1938 to 52 years in 1966, and described the impact of social change on the epidemiological characteristics of endocarditis. Specifically, they reported an increase in staphylococcal and fungal valvular infections related to increasing intravenous narcotic usage. They also found a rising incidence of enterococcal disease, although S. viridans remained the most common causative organism. Rheumatic heart disease was the most common predisposing factor for bacterial endocarditis (38.5% of cases), followed by congenital heart disease (5.8%). Syphilitic heart disease and calcific heart disease each constituted less than 2% of the cases. Murmurs of unknown etiology were present in 24% of patients and 29.8% of the cases were categorized as having no prior heart disease. In particular, they noted that “the older the patient the less frequent is an antecedent history of valvular heart disease.”

In 1978, Garvey and Neu (12) described 154 patients, with a mean age of 55 years, admitted to Columbia-Presbyterian Hospital with 165 episodes of IE from 1968 to 1973. Prosthetic valve infections accounted for 20.6% of the cases; in patients with natural valve endocarditis, aortic involvement exceeded mitral involvement (35–39%). Rheumatic heart disease was again the most common predisposing factor, followed by congenital heart disease, although 65% of the cases for whom information was available had no known underlying cardiac process. Streptococci were the most common organisms producing natural valve endocarditis; however, enterococci and S. aureus accounted for 6.5% and 16% of the cases, respectively. Blood cultures were negative in 11% of the patients. Fever was present in 84% of the cases of natural valve endocarditis, and murmurs were found in 96%. An elevated erythrocyte sedimentation rate was noted in 86% of the cases. Major emboli occurred in 55 of the 107 cases (51.4%) of natural valve bacterial endocarditis, and congestive heart failure was seen in half of the patients in this series. One-fourth of the cases died; of these, the correct diagnosis was not recognized in half.
In 1980, Lowes et al. (13) published the experience of St. Bartholomew’s Hospital, London, from 1966 to 1975. These authors followed 60 patients, 60% of whom were male and 45% of whom were older than 50 years. The predominant underlying heart disease was rheumatic (35%), followed by congenital lesions (22%); however, in 30% of cases no underlying disease was identified. Clinically, only two-thirds of the patients reported fever, but congestive heart failure, cutaneous manifestations, and splenomegaly each occurred in almost half of the cases. During this period, echocardiography was introduced, and six patients were described in whom this procedure localized the site of infection. Blood cultures were positive in 86% of the patients from whom samples were taken, and streptococci accounted for nearly two-thirds of the isolates. Enterococci were reported in seven instances (13%). The overall mortality in this series was 20%, but these authors suggested mortality was higher in patients older than 40 years than in younger patients (25% vs. 10%).

In 1981, Von Reyn et al. (14) surveyed endocarditis at the Beth Israel Hospital in Boston from 1970 to 1977. They reported 104 episodes in 94 patients with a mean age of 57 years. The mean duration of symptoms was 27 days, and a high incidence of underlying valvular heart disease (66%) was noted. The mitral valve was the most common site of infection, accounting for 40% of the cases. Most of the cases were because of S. viridans, and only 5% were culture negative. In addition, 13% of the patients had nosocomial endocarditis, 12% had prosthetic valve infections, and 18% required surgery. A total of 86% of the cases were febrile, 86% had murmurs, and 32% had splenomegaly. The overall mortality was 15%. M-mode echocardiography was performed in 32 patients, 6 of whom demonstrated vegetations.

In 1993, Watanakunakorn and Burkett (15) reported on 210 cases of endocarditis from a large community teaching hospital. Patients in the 60- to 70-year age group accounted for the single largest percentage of cases (29.5%). After excluding intravenous drug users, 46% of the patients had no underlying valve disease. Twenty-eight percent of the cases occurred in individuals with atherosclerotic valves, while only 7% of patients had rheumatic heart disease. Twenty-seven cases (12.9%) occurred in individuals with prosthetic valves. Thirty of the 210 cases (14.3%) were nosocomial and the most common organism was S. aureus (48.6% of non–prosthetic-valve infections in patients who were not intravenous drug users). Fever (66.2%), chills (42.6%), and malaise (39.9%) were the most common symptoms; 81.1% had murmurs. Mortality increased from 10.1% for patients younger than 60 years to 31.5% for patients aged 60 years or older.

In 1995, Hogevik et al. (16) described the epidemiology of endocarditis in 90 Swedish patients. The median age of patients in this series was 69 years, and the authors pointed out that the incidence of endocarditis was more than six times greater in individuals older than 70 years than in those younger than 70 years. Rheumatic heart disease was the predisposing factor in 18% of the episodes, and 15% of the cases occurred in patients with prosthetic valves. Forty-four percent of the patients had no previous history of valvular disease. Importantly, the risk of embolization was lower in patients older than 70 years than in those younger than 70 years. In this series, streptococci were encountered slightly more often (41%) than staphylococci (38%).

In summary, review of data from several large series of IE cases covering the 70-year-period from 1925 to 1995 reveals several notable trends (17–19). First, the average age of patients diagnosed with IE has increased progressively, with an increasing percentage of cases occurring in older adults. Second, the proportion of cases attributable to rheumatic heart disease and congenital heart disease has declined, while the number of cases occurring in the setting of atherosclerotic valvular disease or mitral valve prolapse has increased. In addition, an increasing number of cases are occurring in the absence of
underlying valve disease and in the setting of prosthetic heart valves. Third, although *S. viridans* remains the most common bacterial pathogen, *S. aureus* has emerged as an important cause of IE; in addition, the proportion of culture-negative cases has increased.

**Infective Endocarditis in Older Adults**

In 1896, Gibson remarked on the modified character of the disease in old age, and it has been more than 50 years since Kerr suggested that as the population aged, arteriosclerotic valvular heart disease would become a significant antecedent cardiac lesion for bacterial endocarditis. Thus, it has long been recognized that the clinical features of IE in the elderly differ from those in younger patients. In the next section of this review, we discuss surveys of endocarditis reported in the English literature that have focused on endocarditis in the elderly.

In 1940, Bayles and Lewis (21) reported 28 cases of endocarditis diagnosed at autopsy in people older than 40 years. The authors noted that the majority of cases occurred on valves damaged by rheumatic fever but that 25% occurred on arteriosclerotic valves. They commented on the similarity of the clinical features between younger and older patients, but noted the greater subtlety of the disease in the older group.

In 1945, Zeman and Siegal (22) reported 27 cases of bacterial endocarditis in patients older than 60 years. They emphasized that the features of endocarditis in the older population were more often classified as acute rather than subacute, implying a shorter duration of symptoms and a more aggressive course. Acute disease also suggests the occurrence of infection on previously normal valves, usually caused by *S. aureus*, *Streptococcus pneumoniae*, or group A β-hemolytic streptococci. In recent years, use of the terms “acute” and “subacute” endocarditis has fallen out of favor because of lack of clinical utility. Zeman and Siegal also stressed on the diagnostic difficulties encountered in older patients with bacterial endocarditis because of the frequent occurrence of other underlying disease processes.

In 1949, Traut et al. (23) reported 94 cases of bacterial endocarditis in patients older than 45 years diagnosed at Cook County Hospital in Chicago from 1935 to 1946. The majority of cases (61%) occurred on valves damaged by rheumatic fever, but five occurred on atherosclerotic valves. These authors emphasized the infrequency of the disease in older people. However, in an autopsy series, Wallach et al. (24) described 13 cases of bacterial endocarditis on rheumatic valves and 17 cases on valves without rheumatic disease, all of which occurred in patients older than 50 years. These authors noted that in older patients, IE was more often incidental, not directly related to the cause of death. They further observed that older patients more frequently had underlying genitourinary infections or other diseases (e.g., diabetes mellitus), and more often had sclerotic changes in the valves.

A year later, Anderson et al. (25) described the occurrence of endocarditis in older patients at St. Thomas' Hospital in London. The authors reviewed 14 cases occurring in people older than 60 years (18.4% of the total cases) from 1946 to 1954. Ten patients had *S. viridans* infection and four had either negative cultures or no cultures. Virtually all patients had evening temperatures of 100 °F or higher, and all had murmurs; 43% of the patients had splenomegaly, and the same proportion had cutaneous manifestations. Mortality was higher in older patients than in younger patients (50% vs. 31%). The authors commented that endocarditis was often missed in the elderly because it was not generally recognized that the disease could occur in this age group. In addition, IE in the elderly tended to be less severe, and several criteria usually associated with endocarditis were frequently absent in older patients.
In 1959, Gleck (26) reviewed 10 cases of endocarditis occurring in patients older than 55 years, including six men and four women. In addition to dental extractions and skin infections, genitourinary tract manipulations were precipitating events in the elderly. Only three patients had typical features of endocarditis. Another three patients presented with mental status changes or depression; the other patients presented, respectively, with liver disease, uremia, anorexia and weight loss, and stroke. At least two patients had maximum daily temperatures below 100 °F. Four of the patients with atypical presentations died.

In the same year, Hartman and Myers (27) described seven patients older than 60 years with endocarditis (35% of total cases), of whom four were women. Five patients were infected by \textit{S. viridans}, one by staphylococcus, and one by enterococcus. Four patients had rheumatic heart disease and three had arteriosclerotic disease; two patients died.

In 1960, Cummings et al. (28) noted that 18 of 55 patients with endocarditis were older than 50 years, including 10 women. Murmurs were present in all but three cases and 27% had splenomegaly, but only half were reported to have fever. Streptococcal infections were identified in six patients; in one case \textit{Proteus vulgaris} was isolated from the blood. The remainder had negative cultures or no cultures were drawn. An important finding was that mortality was 72% in the older patients compared with 27% in patients younger than 50 years.

In 1965, Uwaydah and Weinberg (29) noted the changing pattern of endocarditis. Of 100 IE patients seen at the Massachusetts General Hospital in Boston, 38% were older than 60 years, and half of these had infections involving arteriosclerotic or calcified valves. The authors commented on the declining prevalence of rheumatic fever as a predisposition for endocarditis in the older patient. In this series, 37% of the younger patients died, compared with 68% of the older group.

In 1973, Habte-Gabr et al. (30) reported on 57 patients older than 60 years with endocarditis treated at the University of Iowa Hospital from 1940 to 1971. All patients were febrile and half complained of weight loss, confusion, or other symptoms. Overall, signs and symptoms were similar in younger and older patients. The most common organisms isolated from the older age group included \textit{α}-hemolytic streptococcus (40%), other streptococci (23%), and staphylococci (23%); 27% of all patients had negative blood cultures. Among treated patients, mortality was 44%. These authors stressed the increasing incidence and varied presentation of endocarditis in the elderly, especially the high prevalence of central nervous system disturbances and uremia as presenting manifestations.

Watanakunakorn and Tan (31) reported that 19 of 33 cases of staphylococcal endocarditis occurred in people older than 60 years. Presenting complaints were often nonspecific, such as anorexia or mental deterioration. Presaging a modern risk factor for endocarditis, two patients were infected from indwelling intravenous catheters. In 10 patients, the diagnosis was established antemortem from blood cultures; only two of these patients survived. In the other cases, the diagnosis was made at autopsy or by direct culture of surgically removed valves. At autopsy, the mitral valve was the source of infection in 13 of 16 cases and atherosclerosis was the predisposing cardiac condition in 8 of 16 cases.

Watanakunakorn and Tan also reported on 20 patients older than 60 years with \textit{S. viridans} endocarditis (32). The most common presenting complaints of these patients were weakness, fatigue, and weight loss. All patients had fever, all had cardiac murmurs, 40% had splenomegaly, and 60% had cutaneous lesions. In 55% of the patients, the disease involved the mitral valve, in 30% the aortic valve, and in 15% both valves.
Two-year survival was 85%, which was similar to that in younger patients with IE due to *S. viridans*.

In 1974, Applefield and Hornick (33) reported a retrospective analysis of patients admitted to the University of Maryland Hospital between 1950 and 1970 with a diagnosis of endocarditis. Twenty of 29 patients fulfilling the criteria for endocarditis were aged 60 years or older. Among the older individuals, fever of unknown origin was the presenting complaint in 48%; however, 45% presented with neurological findings including delirium. In 10 patients, no murmur was detected. Preexisting aortic and mitral valve abnormalities provided the substrate for infection in 18 and 10 cases, respectively. Staphylococci accounted for 24% of the cases and streptococci for 41% (including three cases of enterococcal disease), but in 29% of the cases no organism was isolated. In the culture-negative group, 72% died, with 48% having received antimicrobial therapy judged to be inappropriate.

Thell et al. (34) presented data on 42 cases of endocarditis occurring in subjects older than 60 years and confirmed by autopsy or surgery. In this series, five cases of right-sided endocarditis were included. The most common organisms were staphylococci in 33% of the cases and streptococci in 24%. Although aortic valve disease was most common in those in whom an underlying process could be identified, no underlying heart disease was found in 37% of the cases. These authors stressed that the diagnosis of endocarditis was suspected in only 38% of the patients despite the fact that fever was present in 94% of those in whom temperature was recorded and murmurs were present in 68%.

Robbins et al. (35) reviewed 56 cases of IE in patients aged 65 years and older. In this group, 93% were febrile, 86% had murmurs, and 36% had peripheral stigmata. All patients tested had an elevated erythrocyte sedimentation rate, and two-thirds were anemic. The cohort was appropriately divided into community-acquired and nosocomially acquired cases. Among 41 community-acquired cases, 71% were due to streptococci, including six cases of *Streptococcus faecalis*; eight cases (20%) were due to staphylococci. Among 15 nosocomially acquired cases, three were due to *S. faecalis*, seven due to staphylococci (six attributed to *S. aureus*), and three due to fungi. Overall, five cases were culture-negative. Underlying diseases predisposing to natural valve endocarditis included 6 cases of rheumatic heart disease, 3 cases of calcific aortic valve disease, and 16 cases of atherosclerotic disease. Complications included congestive heart failure in 36 individuals (64%) and neurological abnormalities in 20 patients (36%). The overall mortality was 45%.

Terpenning et al. (36) compared IE in patients older than 60 years (53 episodes), patients 40 to 60 years of age (46 episodes), and patients younger than 40 years (55 episodes). The proportion of cases caused by streptococci and staphylococci were similar across age groups, but infections due to enterococci, *Streptococcus bovis*, and coagulase-negative staphylococci were more common in the older age group. Among older patients, 23% of infections were nosocomially acquired. In all three age groups, patients with no known heart disease comprised the highest percentage of cases. A slightly greater percentage of the elderly group had prosthetic valves; other underlying causes were similar across age groups. Clinical manifestations were also similar in the various age groups, with fever present in over 80% of patients regardless of age. Confusion was slightly more common in the older age group, while new or changing murmurs were more often noted in the younger groups. Errors in diagnosis were significantly more common in the older group. Echocardiograms demonstrated vegetations in 56.8% of the group younger than 40 years, 47.8% of the group 40 to 60 years of age, and 43.7% of the group older than 60 years. The aortic valve was the most commonly infected valve overall, but
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The mitral valve was more often the site of infection in the elderly (54.7%). In the youngest age group, the tricuspid valve was most often infected because of the higher incidence of intravenous drug use. Major neurological events were slightly more common in the elderly, while pulmonary emboli were more frequent in the younger group. Mortality increased with age, from 9.1% in those younger than 40 years to 28.2% in those aged 40 to 60 years, and 30.2% in those older than 60 years.

In 1994, Durack et al. (37) proposed new criteria for the diagnosis of endocarditis that incorporated the findings of echocardiography. Using these new criteria, Weiner et al. (38) reported on 106 episodes of endocarditis divided into three age groups—younger than 50, 50 to 70, and older than 70 years. The median age of all cases was 59 years. S. viridans and staphylococci were the most common causative organisms in all age groups. While there were no significant differences between age groups with respect to the pathogens identified or the source of infection, elderly patients more often had degenerative and calcified lesions or prosthetic valves. Vegetations identified by echocardiography were smaller in size in the two older groups. Fever (55%) and leukocytosis (25%) were less common in patients older than 70 years compared with those younger than 50 years. Embolic events were more common in the younger group, but other outcomes, including mortality, were similar across age groups.

Selton-Suty et al. (39) also described the clinical and bacteriological characteristics of endocarditis in the elderly using the new echocardiographic criteria. They reported on a total of 114 patients divided into two groups: those older than 70 years and those younger than 70 years. Streptococci were the most common causative organisms in both age groups, but older patients tended to have more infections related to organisms normally inhabiting the gastrointestinal tract. In agreement with earlier studies, elderly patients were more likely to have infections on prosthetic valves (52% vs. 25%) and less likely to experience embolic complications (8% vs. 28%). Mortality was higher in the older than in the younger age group (28% vs. 13%).

In 1998, Gagliardi et al. (40) compared the features of native valve endocarditis in elderly patients with those in younger individuals using the Duke diagnostic criteria. Intravenous drug users were excluded, and patients aged 65 years or older were compared with those aged between 29 and 60 years. Clinical features of the disease were similar in the two age groups but the duration of hospital stay was significantly longer in older patients. The causative organisms, predominantly streptococci and staphylococci, did not differ between age groups, but mitral valve involvement was more common in the elderly, whereas aortic valve involvement occurred more frequently in younger patients. Mortality did not differ between groups.

The following year, Netzer et al. (41) reported on 155 cases admitted to a Swiss referral hospital. Many of the findings were similar to those of Gagliardi et al., but older patients were more prone to complications after valve surgery, and mortality was significantly higher in the elderly—13 of 53 (24.5%) among patients aged 65 years or older versus 9 of 82 (11.0%) for patients younger than 60 years.

In 2003, Di Salvo et al. (42) reported on a series of 315 patients seen at four French and Italian hospitals. Patients were separated into three age categories: younger than 50, 50 to 69, and 70 years or older. Most clinical features were similar between groups except that older patients were less likely to have Osler’s nodes. Elderly patients were more likely to have urinary or digestive tract portals of entry, more likely to have infected pacemakers, and more likely to be anemic. Elderly patients also had a significantly higher mortality rate (17%) than younger patients (10%). In an accompanying editorial, Vahanian (43) noted that patients older than 70 years constituted 26% of endocarditis cases in the Euro Heart Survey on Valvular Heart Disease conducted
in 2001, and that the incidence of endocarditis in a separate French survey peaked between the ages of 70 and 80.

Wang et al. (44) reported on a series of 67 patients aged 65 years and older hospitalized with endocarditis in Taiwan. Twenty of the patients (30%) had nosocomial infections, most commonly caused by staphylococci; hospital mortality in these patients was 30%.

Cruz et al. (45) described 46 episodes of endocarditis in patients aged 65 years or older in Spain. These authors found no significant age-related differences in the manifestations or outcomes of IE. Similarly, Wallace et al. (46) found that age was not an independent predictor of mortality in 220 patients with endocarditis seen at an English tertiary care hospital between 1981 and 1999.

In summary, endocarditis is an evolving process that is increasingly becoming a disease of older patients. This fact is in part related to the declining incidence of rheumatic fever as a predisposing factor in younger patients, leaving age-related degenerative valve disease as a relatively more common risk factor. The greater frequency of gastrointestinal and genitourinary procedures also places the older patient at greater risk for infection with enterococci and other pathogens including gram-negative bacilli. Older patients may be more likely to develop nosocomial infections because of more frequent hospitalizations and age-related immunosenescence. In addition, the increasing number of cardiac valve procedures in older adults, especially aortic valve replacement for severe aortic stenosis, contributes to the rising incidence of prosthetic valve IE in the elderly.

The major clinical manifestations of IE are similar in older and younger patients. Thus, older patients commonly have fever and a heart murmur. Confusion, on the other hand, is a more common symptom of IE in the elderly, and unexplained confusion should prompt a search for an underlying infection, including IE. Peripheral manifestations (petechiae, splinter hemorrhages, Osler’s nodes, Janeway lesions, etc.) occur with approximately equal frequency in older and younger patients, although older patients appear to be less prone to embolic complications. Common laboratory features of IE, including anemia, elevated erythrocyte sedimentation rate, and hematuria also appear to occur with equal frequency across the age spectrum.

The diagnosis of endocarditis in older adults is often delayed in part because clinicians are less apt to consider it. Generally, the sensitivity and specificity of the Duke criteria for establishing a diagnosis of IE do not appear to be affected by age. Blood cultures taken before empirical antibiotics, especially if endocarditis is a consideration, are crucial. Echocardiography (47) is useful for identifying valve pathology and assessing overall cardiac performance. Vegetations are visualized by transthoracic echocardiography in approximately 50% of the cases with proven IE. In patients for whom there is a moderate to high clinical suspicion for IE but who have a negative transthoracic echocardiogram for vegetations, transesophageal echocardiography should be performed, as the sensitivity of this technique approaches 90% (48).

The clinical course of IE in older patients differs in several respects from that in younger patients. As noted above, embolic complications are less common in the elderly; conversely, neurological complications occur more frequently in older patients. In most, but not all studies, mortality rates have been higher in older compared with younger patients (42,49). In addition, the effect of age on mortality may in part depend on the nature of the underlying valve pathology and the bacterial pathogen involved. Thus, outcomes may be similar in older and younger patients with mitral valve prolapse infected by *S. viridans*, whereas mortality may indeed be higher in older patients with more severe infections (e.g., enterococci or methicillin-resistant staphylococci) involving degenerative valves with significant stenosis or regurgitation.
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The treatment of endocarditis in older patients is similar to that in younger individuals (9). However, because older individuals are more likely to have multiple comorbid conditions, especially chronic renal insufficiency, and more likely to be taking multiple medications, care must be exerted when using potentially toxic agents (e.g., aminoglycosides). Greater vigilance is also required in monitoring renal function and assessing for drug toxicity and drug interactions. It is still important to measure the minimum inhibitory concentration for the infecting bacteria and, when possible, it is also useful to measure the minimum bacteriocidal concentration. For resistant organisms, such as methicillin-resistant *S. aureus*, serum drug levels should be obtained to ensure that the organism will be effectively eradicated.

With these caveats, suggested regimens for the treatment of endocarditis are listed in Table 1 (17,49,50). Prophylaxis for prevention of bacterial endocarditis in older patients is identical to that recommended for younger patients (49,51).

The role of surgical intervention for the treatment of IE continues to evolve. Indications for surgery include microbiological failure, recurrent embolization, severe hemodynamic compromise due to valvular dysfunction, abscess formation (especially common with *S. aureus*), and very large vegetations (>1 cm, often due to a fungal

### Table 1 Regimens for the Treatment of Infective Endocarditis

<table>
<thead>
<tr>
<th>Etiology</th>
<th>Treatment</th>
<th>Duration (wk)</th>
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<tbody>
<tr>
<td>Natural valve endocarditis</td>
<td></td>
<td></td>
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<tr>
<td><em>S. viridans</em></td>
<td>Penicillin G 10–20 million U/day (divided dose) plus gentamicin 3 mg/kg/day</td>
<td>4 wk</td>
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<tr>
<td>Enterococci</td>
<td>Ampicillin 12 g/day plus gentamicin 3 mg/kg/day (divided doses) or Vancomycin* 500–1000 mg twice per day and gentamicin 3 mg/kg/day (divided doses)</td>
<td>6 wk</td>
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<tr>
<td>Staphylococci</td>
<td></td>
<td></td>
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<tr>
<td>Coagulase-positive (methicillin-sensitive)</td>
<td>Nafcillin 12 g/day (divided dose)</td>
<td>6 wk</td>
</tr>
<tr>
<td>Coagulase-negative (methicillin-resistant)</td>
<td>Vancomycin* 500–1000 mg twice per day</td>
<td>6 wk</td>
</tr>
<tr>
<td>Fastidious gram-negative rods (e.g., HACEK* organisms)</td>
<td>Ceftriaxone 2g/day</td>
<td>6 wk</td>
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<tr>
<td>Prosthetic valve endocarditis</td>
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<tr>
<td>Coagulase-negative or coagulase-positive staphylococci</td>
<td>Vancomycin 500–1000 mg twice per day plus gentamicin 3 mg/kg/day (divided doses) or rifampin 300 mg/day</td>
<td>6 wk</td>
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</table>

*All doses are intravenous unless otherwise indicated.

*aVancomycin 30 mg/kg per 24 hr in two divided doses not to exceed 2 g in 24 hr unless serum levels are monitored.

*HACEK (Hemophilus parainfluenza, Hemophilus aphrophilus, Hemophilus paraphrophilus, Actinobacillus actinomycetemcomitans, Cardiobacterium hominis, Eikinella corroden, and Kingella kingae).
organism). Recent data indicate that in properly selected older patients with IE, surgery can be performed with acceptable risk and favorable effects on long-term outcomes (52–54), although perioperative mortality appears higher in patients older than 65 years (52).

REFERENCES

Infective Endocarditis in the Elderly


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Cardiomyopathies in the Elderly

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The true prevalence of cardiomyopathy in the elderly may be underestimated because of the low sensitivity of the clinical criteria, particularly in milder cases. Data from the Framingham study demonstrate that the incidence of heart failure is 10% in patients older than 80 years of age as compared with only 1% in patients who are in their sixth decade (1). Approximately one-third of those identified expire within two years of diagnosis. The annual incidence in men aged 85 to 95 years was noted to be 4.4%, with a doubling of incidence noted with each 10 years of age, making heart failure the leading primary diagnosis in hospitalized elderly patients (1,2). This chapter focuses on the nonischemic causes for cardiomyopathy encountered commonly in the elderly.

DIASTOLIC DYSFUNCTION

Diastolic dysfunction is especially prevalent in the elderly and accounts for a very high morbidity and mortality (3,4). Of patients identified as having congestive failure by the Framingham study, more than 50% had a left ventricular (LV) ejection fraction greater than 50% (5). Mortality, although lower than that noted for patients with diminished ejection fraction, remained four times greater than that of age- and sex-matched controls. A recent 15-year study of 4596 elderly patients performed at the Mayo Clinic demonstrated that the prevalence of heart failure with a preserved ejection fraction increased significantly between 1986 and 2002 (6). An analysis of 83 patients with clinical heart failure and LV ejection fractions greater than or equal to 45% participating in the Vasodilator-Heart Failure Trial (V-HeFT) has previously demonstrated that exercise
tolerance in this population was only slightly better than that for patients with lower ejection fractions (7).

The pathophysiology of diastolic dysfunction combines delayed relaxation, impairment of LV filling, and decreased compliance of the ventricle (8). Delayed relaxation, or more properly prolonged systolic contraction, can be induced by any substance that will increase the pressure or volume load to the ventricle, such as angiotensin II or antidiuretic hormone. While, delayed relaxation represents a compensatory adjustment to loading phenomena, impaired relaxation with secondary reduction in ventricular filling constitutes active diastolic pathology that relates to a specific underlying cause. It is important to recognize that diastolic dysfunction is, to some extent, a function of aging per se, perhaps related to an increase in cellular apoptosis over time (9,10). This tendency toward diastolic dysfunction with aging has been demonstrated to be reversible with exercise in an animal model (11). Recent studies in humans have also demonstrated that patients presenting with heart failure and preserved ejection fraction manifest ventricular systolic and arterial stiffening in excess of that associated with aging or hypertension (12). As a result, the clinician must be able to differentiate between what could be a result of normal sedentary aging and abnormal deterioration in ventricular compliance. Specific therapies that have been investigated in a preliminary fashion for patients with heart failure and preserved LV systolic function include AT, receptor blockade, statin therapy, and aldosterone antagonism (13–15). Pathologically, diastolic dysfunction with normal LV systolic dysfunction is associated with coronary artery disease (see chaps. 9–16), restrictive cardiomyopathy, and both primary and secondary hypertrophic cardiomyopathy.

RESTRICTIVE CARDIOMYOPATHY

Restrictive cardiomyopathy results from increased stiffness of the LV myocardium, generally as a result of infiltrative disease (16). As the infiltrative disorder is often biventricular, right-sided signs often predominate. Disturbances in conduction as well as dysrhythmia can also be common (17–20). Clinical findings are often similar to pericardial constriction, and care is required in order to establish the correct diagnosis (21).

Etiology

In contrast to younger patients, idiopathic restrictive myopathy is not only rare in the elderly, but also carries a better prognosis (22). Similarly, Löffler’s endocarditis is extremely rare in older populations (23). Amyloidosis constitutes the most common etiology in the elderly, followed by other infiltrative processes such as cardiac sarcoid, carcinoid, hemochromatosis, and systemic sclerosis (9,24). The broader use of both chest radiotherapy and anthracyclines in elderly patients with cancer leaves these patients at the risk of developing restrictive cardiomyopathy secondary to endomyocardial fibrosis (25).

Amyloid infiltration of the atria is extremely common in the elderly and has been documented in 91% of subjects of advanced age in a recent histological study (26). Primary amyloidosis, manifesting as a clinical syndrome with cardiac involvement, however, is considerably less common. The incidence of primary amyloidosis has been estimated to be between 6.1 and 10.5 per million person-years with the median age of presentation to medical attention being roughly 74 years (27). Diastolic dysfunction associated with primary amyloidosis may result directly from the presence of monoclonal immunoglobulins rather than requiring the presence of the amyloid deposit itself. A recent study demonstrates that diastolic dysfunction similar to that observed in patients with
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Figure 1 Two-dimensional echocardiogram from a parasternal long-axis view in an elderly patient with cardiac amyloidosis shows a hypertrophic interventricular septum with the characteristic “sparkling” appearance of the septal myocardium. Abbreviations: RV, right ventricle; IVS, interventricular septum; AO, aorta; LA, left atrium; MV, mitral valve; LV, left ventricle; PW, posterior wall.

Cardiac involvement can be replicated in mice simply by the systemic infusion of light chains isolated from patients with cardiac amyloidosis (28).

The ventricular cavities are generally normal or small in size; however, mild dilatation can be noted (Fig. 1). The atria are characteristically dilated and in some cases may present with thrombi in the appendages (25). Only 25% of patients with primary amyloidosis present with congestive heart failure, while about one-sixth present with orthostatic hypotension (24). Median survival in patients presenting with congestive heart failure is six months. One of the key prognostic variables is LV wall thickness. Median survival is 2.4 years for patients presenting with normal ventricular dimensions and falls to 0.4 years for those with significant LV hypertrophy (LVH) (29,30). Prognosis is also reduced in patients presenting with shortened deceleration time and an increase in the E/A ratio as measured by Doppler echocardiography (Fig. 2) (31). Dysrhythmia associated with amyloidosis ranges from node dysfunction and bundle branch blocks to life-threatening ventricular dysrhythmia and is also related to the severity of the disease process as demonstrated by the above indices (32).

Familial amyloidosis, although responsible for only 10% of cases, also presents in the elderly. This autosomal dominant disorder is indistinguishable from primary amyloidosis by clinical criteria and requires identification of the variant protein by immunochemical modalities. Accurate diagnosis is important primarily because of the more favorable prognosis for survival, which is roughly twice that of primary amyloidosis (33).

Cardiac sarcoidosis is associated with interstitial inflammation resulting in abnormal diastolic function (34). Incidence and prevalence of cardiac involvement remains largely unknown with only a minority of patients presenting in their elder years. Cardiac involvement can apparently be frequently subclinical with studies demonstrating between five and eight times as many patients presenting with cardiac infiltration at
necropsy as had been previously diagnosed clinically (35,36). As many as half the patients presenting with sarcoidosis can have electrocardiographic abnormalities; however, the precise significance of these findings is unknown (37). Sudden death is the most common cause of mortality in patients presenting with cardiac sarcoid as a result of either complete heart block or malignant tachyarrhythmia (38).

The mean age of patients presenting with carcinoid syndrome has been reported to be 64 years with a range extending up to 83 years (39). Up to half of the cases present with carcinoid heart disease as a late complication (40). The majority of cases present with tricuspid regurgitation with additional fibrotic involvement of the pulmonic valve and the right ventricular endocardium.

Presentation and Diagnosis

Restrictive myopathies often present with generalized findings of fatigue, peripheral edema, paroxysmal nocturnal dyspnea, orthopnea, dyspnea, and occasionally, ascites. Chest pain can occur in patients presenting with amyloidosis (41). Similar clinical presentations require that this diagnosis be differentiated from pericardial constriction. This task is accomplished largely by a combination of clinical history with echocardiographic and Doppler findings, cardiac magnetic resonance imaging, and hemodynamic observations. Similar to pericardial constriction, restrictive myopathy often presents with a prominent y descent in the jugular venous pulse, a positive Kussmaul’s sign, an enlarged and pulsatile liver, ascites, and pedal edema. The presence of a third heart sound can serve to help differentiate restriction from constriction, which classically presents with a pericardial knock. The presence of pulmonary alveolar congestion on chest radiography favors restriction over constriction.
The classic echocardiographic presentation of amyloid heart disease includes LVH with characteristic sparkling of the myocardium (42). Mitral inflow velocities in patients with diastolic dysfunction vary depending on the extent of the disease. E/A ratios in the elderly customarily become less than one in most individuals. The first sign of diastolic dysfunction is often pseudonormalization of the Doppler spectral display in which the E/A ratio once again becomes greater than one associated with increasing prominence of the diastolic filling velocity in the pulmonary vein (43,44). Active restrictive physiology results in a very steep, high-velocity mitral E-wave with a short deceleration time, followed by a very small or absent A-wave (25). B-natriuretic peptide assay has recently been used to enhance the diagnosis of diastolic dysfunction in patients who present with normal systolic function on echocardiography (45).

Thickening of the pericardium, which is common in pericardial constriction, is absent in patients with restrictive cardiomyopathy on cardiac magnetic resonance imaging. At cardiac catheterization, the end-diastolic pressures can be equalized in both restrictive and constrictive physiology; however, it is rare for the pre–A pressure to fall toward zero in patients with restriction. In some patients, endomyocardial biopsy may be necessary for diagnosis (46).

Treatment
Specific therapy for patients with restrictive myopathy is poorly understood (47). Drug therapy has been primarily aimed at the presumed cause of the disorder (8). In patients in whom tachycardia appears to play a major role, the use of β-blockade, some calcium channel blockers, and occasionally digoxin has been advocated. Angiotensin-converting-enzyme inhibitors have been used to reduce both pressure and volume load as well as assist in ventricular remodeling at the microstructural level (8). Diuretics reduce preload and improve exercise tolerance (48). Nitrates similarly decrease preload as well as potentially abbreviate systole, which could assist in the augmentation of diastolic filling (49,50). Warfarin may be indicated in those patients who present with atrial appendage thrombus on transesophageal echocardiography. Drugs such as amiodarone may be necessary to maintain sinus rhythm and enhance cardiac output in patients who develop atrial fibrillation (25). Pacing may be a requisite for patients who develop conduction system disease (51).

HYPERTROPHIC CARDIOMYOPATHY

Hypertrophic cardiomyopathies are common in the elderly. In some series, more than 80% of patients presenting to the hospital with newly diagnosed hypertrophic obstructive cardiomyopathy (HOCM) were older than 50 years of age and more than 40% were older than 60 years of age (52,53). Hypertensive hypertrophic cardiomyopathy is characteristically found in older populations. Whereas older males and females demonstrate generally equal prevalence of obstructive cardiomyopathy, hypertensive hypertrophic cardiomyopathy appears to predominate in females (53,54).

Hypertrophic cardiomyopathy in older adults needs to be differentiated from the septal bulge or “sigmoid septum” commonly seen in older patients without any other evidence of myocardial hypertrophy (55). The bulge is caused by an increased angulation of the interventricular septum, which can result in as much as a twofold increase in LV outflow tract velocity following amyl nitrate. A recent echocardiographic study has documented that, although demonstrating an increase in fractional shortening comparable
to a patient with hypertrophic cardiomyopathy, subjects with septal bulge had no decrease in end-diastolic dimension, no evidence of anterior malposition, and normal wall thickness apart from the basal septum, suggesting that this constitutes a separate physiological entity (56).

HOCM

HOCM has an autosomal dominant inheritance pattern with many different mutations, some of which are specific to phenotypic expression at an older age (57–59). Although disease severity can vary depending upon the type of mutation, phenotypic expression varies to such a degree as to currently render the type of mutation a poor indicator of prognosis on a case-by-case basis (60,61). The histological pattern of HO CM has been demonstrated to be distinctly different from the hypertrophy associated with hypertension (62).

Elderly patients diagnosed with HO CM present with an increased severity of symptoms compared to younger individuals; however, the progression of the disease appears to be slower with 23% of elderly patients achieving a normal life expectancy, in a recent study (53,63–65). The annual mortality for the elderly patient with HO CM has been reported to be only 2.6% compared with 5.9% in younger patients, and does not appear to be demonstrably different from that of age- and sex-matched controls (54,66). A significant increase in baseline LV mass measured by either echocardiography or electrocardiography has been associated with a decrease in ejection fraction over time in a cohort of elderly patients (67).

The predominant symptom noted by multiple authors is dyspnea with between one-third and one-half of elderly patients presenting with chest pain (54,64,68,69). Presentation in New York Heart Association class III or IV heart failure has been noted to increase the annual mortality rate to 36% (54). Between 20% and 30% of patients complain of syncope or presyncope, while some authors report palpitations in as many as half (54,64,66). Classic physical findings include the presence of carotid pulsus bisferiens, a fourth heart sound, and a systolic ejection murmur at the left sternal margin that becomes more prominent with the Valsalva maneuver and less audible with isometric exercise (70,71). The bisferiens pulse may be less noticeable in older patients as a result of increased atherosclerosis in the peripheral vasculature (64,72). Both atrial fibrillation and hypertension have been reported to be more commonly associated with the diagnosis in the elderly, and are also associated with decreased survival (66,73). Electrocardiographic presentation in the older adult includes the presence of atrial abnormality, LVH, and bundle branch block; however, the anterior Q waves that are typical of HO CM in the young are only rarely seen (66,74).

Echocardiographic findings in the elderly patient with HO CM, similar to younger patients, include LVH, systolic anterior motion (SAM) of the anterior leaflet of the mitral valve, and increased LV outflow tract velocity (Figs. 3–12) (72). LV cavity shape in the elderly appears to be more oval than that of younger patients with HO CM (64). In addition, mitral annular calcification is much more common in older patients presenting with HO CM, with prevalence rates reported to be anywhere between 30% and 100% (75–78). As a result, the mechanism for outflow tract obstruction may depend more on the posterior displacement of the septum and less on the anterior displacement of the mitral apparatus than it does in younger patients.

β-Adrenergic blocking agents and nondihydropyridine calcium channel blockers, particularly verapamil, have been shown to reduce symptoms in patients with HO CM;
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Figure 3  Systolic frame of a two-dimensional echocardiogram from an apical view in a 91-year-old female with hypertrophic cardiomyopathy of the elderly, showing extensive mitral annulus calcification and prominent systolic anterior motion of the mitral valve with near obliteration of the LVOT. Abbreviations: LVOT, left ventricular outflow tract; SAM, systolic anterior motion of the mitral valve leaflets; MAC, mitral annulus calcification.

Figure 4  Early systolic frame from a two-dimensional parasternal long axis view in the same patient illustrated in Figure 3, showing a prominent septal bulge and systolic anterior motion of the mitral valve. Abbreviations: RV, right ventricular cavity; IVS, interventricular septum; Ao, aortic root; LV, left ventricular cavity; LA, left atrium; PW, posterior wall; MAC, mitral annulus calcification; SAM, systolic anterior motion of the mitral valve leaflets.
Figure 5  Color Doppler flow display superimposed on the same systolic frame from a parasternal long axis view shown in Figure 4, demonstrating turbulent LVOT flow. **Abbreviations:** RV, right ventricle; IVS, interventricular septum; LA, left atrium; MV, mitral valve; LV, left ventricle; PW, posterior wall; LVOT, left ventricular outflow tract.

Figure 6  CW Doppler obtained from interrogation of the LVOT flow in the same patient illustrated in Figure 3, demonstrating a large increase of LVOT velocity (maximum \( \approx 6 \text{ m/sec} \)) and a Bernoulli-derived gradient of 170 mmHg. **Abbreviation:** LVOT, left ventricular outflow tract.
Figure 7 M-mode echocardiogram at the mitral valve level in an elderly patient with obstructive hypertrophic cardiomyopathy. During midsystole, a smooth anterior motion at the mitral valve is noted. The mitral valve assumes a flattened curve appearance as it approaches the septum, and the contact with the septum is facilitated by the posterior motion of the septum. Mitral annular calcification is present behind the posterior leaflet. Abbreviations: IVS, interventricular septum; RV, right ventricular cavity; MV, mitral valve; CA ANNUL, mitral annular calcification.

Figure 8 Diastolic frame of a two-dimensional echocardiogram from a parasternal long-axis view in an elderly patient with hypertrophic cardiomyopathy shows a small LV chamber, a hypertrophic interventricular septum (IVS), a fibrotic mitral valve (MV), and a calcified mitral annulus (Ca). Abbreviation: LV, left ventricle.
Figure 9  Two-dimensional apical four-chamber systolic still frame from an elderly patient with obstructive hypertrophic cardiomyopathy shows hypertrophy of the interventricular septum (IVS), a small LV cavity, fibrotic mitral valve (MV) leaflets, and a calcified mitral annulus (Ca). *Abbreviation:* LV, left ventricle.

Figure 10  LV diastolic waveforms obtained with pulsed Doppler echocardiography in an elderly patient with hypertrophic cardiomyopathy show reduced maximal flow velocity of early peak (E), slow deceleration of early diastolic flow velocity (from E to F), prolongation of early filling components (from D to F) at the expense of diastasis, and increased maximal velocity of the late peak as a result of atrial systole (A). *Abbreviation:* LV, left ventricle.
Figure 11  Color Doppler flow display from a patient with obstructive hypertrophic cardiomyopathy shows turbulent flow in the LVOT and mild mitral regurgitation (MR). (See color insert). Abbreviation: LVOT, left ventricular outflow tract.
however, no clear effect on mortality has been documented (70,79). As in patients with coronary disease, hypersensitivity to β-adrenergic stimulation accompanied by precipitous clinical deterioration occurs in patients who are abruptly withdrawn from β blockers (80). Patients who do not respond to β-blockade can have a salutary response to large doses of verapamil (81). Controlled release disopyramide in doses of 150 to 900 mg daily has also been demonstrated to decrease symptoms in as many as 66% of patients, with a reduction in subaortic gradient of approximately 50% over three years (82). All of these agents are relatively contraindicated in patients with conduction system disease in the absence of cardiac pacing. Positive inotropic agents such as digoxin and load-reducing agents such as nitrates, diuretics, and dihydropyridine calcium channel blockers are relatively contraindicated because of their ability to increase the gradient across the LV outflow tract (53,74,78).

Dysrhythmia requires special attention in this patient population. Atrial fibrillation is associated with a diminished long-term prognosis and requires anticoagulation (83). Ventricular dysrhythmia poses a more vexing problem. A recent trial has demonstrated that ventricular tachycardia or fibrillation appears to be the primary mechanism for sudden death in patients carrying a diagnosis of hypertrophic cardiomyopathy (84). In these cases, implantable defibrillators were found to be efficacious in the treatment of these rhythms and the prevention of sudden death. Mean age in this patient population, however, was 40 ± 16 years with more than half the sample size younger than 41 years. In addition, it is not clear how many of these subjects presented with HOCM and how many had hypertensive hypertrophic cardiomyopathy, although the mean age suggests that HOCM might have been the prevailing diagnosis. A subsequent trial demonstrated that LV wall thickness is directly related to the risk of sudden death and may, therefore, be an indicator of the need for automatic implantable cardioverter-defibrillator placement (85).
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Once again, however, the mean age was only 47 years with the mean age being youngest (31 years) for the patients with the thickest walls. As a result, it is unclear at this time how much prescriptive relevance these data have for the older patient with obstructive myopathy. These findings in combination with other observations (vide infra), however, suggest that the appearance of complex ventricular dysrhythmia in the elderly patient with hypertrophic cardiomyopathy does, in fact, suggest a negative prognosis in comparison to patients in whom they do not appear, and these patients should be considered for cardioverter defibrillator placement.

Dual-chamber pacing for patients with HOCM who have not responded to medical therapy has been associated with variable results (86–88). Maron et al. demonstrated a significant reduction in outflow tract velocity in all subjects; however this finding did not translate into improved functional capacity for any subgroup except for elderly patients older than 65 years (89). As such, pacing may be of some benefit to older adults with HOCM who do not respond well to medical therapy.

In patients who continue to demonstrate class III or IV symptoms, despite medication and pacing, surgery or transcatheter septal ablation must be considered. Older studies have described symptomatic improvement in as many as 80% to 90% of patients older than 65 years undergoing surgical myectomy (31,64). Operative mortality, however, has been observed to more than triple in patients older than 65 years when myectomy is combined with coronary artery bypass surgery (90). The concurrent presence of severe mitral annular calcification may require mitral valve surgery as well (77). More recent data from a three-patient subset of patients with HOCM and mitral annular calcification undergoing myectomy (mean age = 61 years) suggests that the myectomy alone may significantly reduce the amount of mitral regurgitation such that mitral surgery may be unnecessary (91). Initial one-year follow-up of patients with HOCM as old as 83 years undergoing transcatheter septal ablation with ethanol has been favorable (92). Therefore, this procedure may be an acceptable alternative to surgical intervention in selected cases.

Hypertensive Hypertrophic Cardiomyopathy of the Elderly

Topol and colleagues, who reported on 21 elderly patients in 1985, first described hypertensive hypertrophic cardiomyopathy (HHC) (93). There has been significant concern as to whether or not this description represents a genuinely different pathophysiological entity from other hypertrophic myopathies (94). A more recent study has suggested that the cell cycle is actively deranged in patients (mean age 61 years) with nonhypertensive cardiomyopathy compared to patients with hypertensive LVH (95). Similarly, therapy with captopril was associated with regression of ventricular hypertrophy in hypertensive patients, but not in nonhypertensive patients with cardiomyopathy. As such, the pathophysiology of the two groups of patients appears to be different. Patients with HHC may represent a hybrid of pathology that superimposes aspects of hypertensive LVH on a genetic predisposition to primary hypertrophic cardiomyopathy (96). In contradistinction to HOCM, sudden death in this patient population appears to be rare, while prognosis for survival in general appears to be better (93).

Patients with hypertensive hypertrophic cardiomyopathy classically present with flash pulmonary edema in the absence of prior symptoms (53). Although frequently presenting with a chronic history of hypertension, the extent of the blood pressure elevation often does not correlate with the severity of the ventricular hypertrophy (93). The findings on physical examination are somewhat similar to HOCM and feature the absence of neck vein distension, a palpable S4, a LV heave, and a systolic ejection murmur (97). The echocardiogram demonstrates severe LVH with hyperdynamic
contractility and cavity obliteration, left atrial dilatation, and delayed opening of the mitral valve. Concentric LVH is more commonly seen than asymmetric septal hypertrophy, and SAM is present in less than one-third of cases (53,93,95).

Medical therapy for patients with HHC is similar to that of patients with HOCM, with the exception that the need for diuretic therapy may be somewhat greater as a result of recurrent episodes of pulmonary edema.

**DILATED CARDIOMYOPATHY**

Idiopathic dilated cardiomyopathy is primarily a disease of ventricular muscle, with increased LV or biventricular volumes, without an appropriate increase in ventricular septal or free wall thickness, and with depression of LV systolic function (98). Other etiological factors that can cause diffuse LV systolic dysfunction must be excluded (99).

In a large cohort of 554 unselected men and 1243 women aged older than 60 years in a long-term healthcare facility, the prevalence of idiopathic dilated cardiomyopathy was 1% for both sexes (100). In the same cohort, the prevalence of abnormal LV ejection fraction (<50%) was 29% in men and 21% in women. Approximately 10% of patients with dilated cardiomyopathy are older than 65 years of age (101–104). The diagnosis of dilated cardiomyopathy can be confirmed by echocardiography (Figs. 13–15), and by pulsed Doppler echocardiography (Fig. 16) in elderly patients. Figure 15 shows a large apical thrombus that can complicate this condition. Coronary angiography should be considered in patients with dilated cardiomyopathy and chest pain. Transthoracic coronary echocardiography has been proposed as a useful method for distinguishing between ischemic and nonischemic dilated cardiomyopathy (105).

![Figure 13](image)

*Figure 13* M-mode echocardiogram at the mitral valve level in an elderly patient with dilated cardiomyopathy shows thinning of the interventricular septum (IVS), a markedly dilated LV cavity (LV), and increased E point septal separation. Abbreviations: LV, left ventricle; RV, right ventricle; MV, mitral valve; PW, posterior wall.
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Figure 14 Diastole frame of a two-dimensional echocardiogram from a parasternal long-axis view in an elderly patient with dilated hypertrophic cardiomyopathy shows thinning of the interventricular septum (IVS) and a large LV cavity (LV). Abbreviations: LV, left ventricle; RV, right ventricle; AO, aorta; MV, mitral valve; PW, posterior wall; LA, left atrium.

Figure 15 Two-dimensional apical two-chamber view in an elderly patient with dilated cardiomyopathy shows a large apical thrombus. Abbreviations: LV, left ventricle; IW, inferior wall; MV, mitral valve.
Symptoms

Symptoms due to dilated cardiomyopathy include fatigue and weakness resulting from decreased cardiac output, exercise intolerance, dyspnea due to pulmonary congestion, chest pain, and syncope. Symptoms due to systemic or pulmonary emboli may also occur. Physical examination reveals moderate-to-severe cardiomegaly and audible third and fourth heart sounds. Signs of LV or biventricular failure may be present.

Fuster et al. reported 104 patients at the Mayo Clinic with idiopathic dilated cardiomyopathy followed for 6 to 20 years (103). Of these 104 patients, 73% had congestive heart failure at the time of diagnosis, and 96% had congestive heart failure at follow-up. Systemic emboli were present in 4% of the patients at the time of diagnosis and in 18% of the patients at follow-up. Systemic thromboembolism developed in 8 of 24 patients (33%) with atrial fibrillation and in 11 of 80 patients (14%) with sinus rhythm ($p = NS$). Systemic thromboembolism developed in 18% of patients who did not receive anticoagulant therapy and in none of those who did ($p = 0.05$). Of 104 patients, 80 (77%) had died at follow-up, two-thirds of the deaths having occurred within two years.

Roberts et al. reported that 148 of 152 necropsy patients (97%) with idiopathic dilated cardiomyopathy had clinical evidence of chronic congestive heart failure (104). Sudden death was the initial manifestation in 114 of 152 patients (75%), and in most patients, ventricular dysrhythmia became intractable and caused death. The mean duration from the onset of chronic congestive heart failure to known death in 120 patients was 54 months. The cause of death was chronic congestive heart failure in 58% of patients, sudden death in 27% of patients, pulmonary emboli in 9% of patients, and other in 6% of patients.

Figure 16  LV diastolic waveforms obtained with pulsed Doppler echocardiography in an elderly patient with dilated cardiomyopathy show increased flow velocity of early peak ($E$), fast deceleration of early diastolic flow velocity from ($E$ to $F$), shortening of early diastolic filling component from ($D$ to $F$) with visible diastasis, and decreased maximal velocity of the late peak as a result of atrial systole ($A$).
Clinical evidence of pulmonary emboli was present in 39% of patients. Clinical evidence of systemic emboli was present in 20% of patients. Of 131 patients, 79 (60%) had either clinical or necropsy evidence, or both, of pulmonary or systemic emboli.

Falk et al., studying 25 patients with nonischemic dilated cardiomyopathy who were not receiving anticoagulant therapy, demonstrated that a LV thrombus was present on initial echocardiogram in 11 patients (44%), developed during 21.5 months of follow-up in an additional four patients (16%), and disappeared in two patients (8%) during follow-up (106). Systemic thromboembolism developed in 5 of 25 patients (20%) during follow-up. Of the five thromboembolic events, four occurred in patients with echocardiographic evidence of a LV thrombus. These five patients with thromboembolic events were treated with warfarin. No further embolic events occurred in these patients at 15 months of follow-up.

**Therapy**

Congestive heart failure in patients with dilated cardiomyopathy should be treated with salt restriction, diuretics, and angiotensin-converting enzyme (ACE) inhibitor therapy. Of interest is the observation that elderly hypertensive patients enrolled in the Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT) who were treated with a thiazide diuretic were less likely to develop heart failure than patients treated with an ACE inhibitor (107). Digoxin has been demonstrated to reduce the number of hospital admissions due to heart failure; however, its effect on total mortality appears to be neutral (108). An analysis of a combination of data from both the Randomized Assessment of Digoxin and Inhibitors of Angiotensin-Converting Enzyme (RADIANCE) and the Prospective Randomized Study of Ventricular Failure and Efficacy of Digoxin (PROVED) databases found that the effect of digoxin on clinical outcome was identical even at low serum digoxin levels (0.5 to 0.9 ng/mL) (109). A subsequent post hoc analysis of data from the Digitalis Investigation Group trial has recently suggested that there may be a survival benefit conferred on patients with serum digoxin levels less than 1 ng/mL (110). A second post hoc analysis of the same data also suggested an increase in mortality in women with congestive failure taking digoxin; however, a subsequent independent analysis demonstrated no increase in mortality in women with digoxin levels less than 1 ng/mL (111,112). An analysis of the effect of increasing age on patients in the Digitalis Investigation Group database specifically found that advanced age per se was not associated with an increased risk for digoxin intoxication (113).

β-blockade has now been shown unequivocally to be associated with improvement in symptoms, quality of life, exercise capacity, ejection fraction, and survival (114–118). This observation has been attributed to an increase in β1-adrenergic receptor density, prolongation of the action potential with secondary increase in calcium influx, and induction of changes in gene expression (119). Recent work has demonstrated that β-blockade also enhances calcium release channel function as well as increases plasma B-type natriuretic peptides in patients with heart failure (120,121). β blockers have also recently been demonstrated to improve contractile dyssynchrony in patients with heart failure who have narrow QRS complexes (122).

Beneficial effects have also been observed in patients with heart failure treated with spironolactone, allopurinol, and AT1 blockade (118,123,124). The role of anticoagulants in the patient population presenting with sinus rhythm and LV dysfunction is unclear, with some sources suggesting this for severe LV dysfunction (vide supra). There is no evidence that antiarrhythmic drugs prolong life or prevent sudden cardiac death in
patients with dilated cardiomyopathy; however there is clearly increased survival
associated with automatic implantable cardioverter-defibrillator therapy in patients with
dilated cardiomyopathy and a low ejection fraction (125). Cardiac resynchronization
therapy with biventricular pacing has been shown to be of value in reducing symptoms,
improving exercise capacity, reducing complications, and reducing mortality in patients
with advanced heart failure, a wide QRS complex, and evidence of contraction
dyssynchrony (126). There is also some evidence that biventricular pacing also improves
symptoms and reverses remodeling in patients with heart failure, evidence of LV
dyssynchrony on echocardiography, and narrow QRS complexes (127).

The use of natriuretic peptides for the treatment of decompensated heart failure has
been controversial. Although in-hospital mortality is apparently reduced in patients with
decompensated heart failure at a mean hospitalization of 7.9 days with the use of the
natriuretic peptide, nesiritide, when compared to therapy with positive inotropes, a meta-
analysis of three trials suggests that mortality at 30 days is increased in patients treated
with nesiritide (128,129). A meta-analysis of five trials has also demonstrated a decrease
in renal function associated with the use of nesiritide (130).

Additional potential therapies for dilated cardiomyopathy include enhanced external
counterpulsation, the use of vasopressin antagonists, and the intriguing possibility of H2
receptor blockade. Enhanced external counterpulsation has been shown to improve
exercise tolerance and New York Heart Association functional classification in patients
with dilated cardiomyopathy as well as patients with ischemic disease (131). Tolvaptan, a
vasopressin antagonist, has been shown to improve volume loss as well as sodium levels
in patients hospitalized with heart failure (132). The H2 receptor blocker famotidine has
been demonstrated to improve symptoms and ventricular remodeling at 24 weeks in a
relatively small series of patients, nearly half of which presented with dilated
cardiomyopathy (133). Further investigation will be requisite before long-term efficacy
and safety can be assessed.

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Thyroid Heart Disease in the Elderly

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INTRODUCTION

The cardiovascular manifestations of thyroid disease are well documented and may lead to clinical diagnosis of thyroid dysfunction. Although the effects of severe thyroid disease have been increasingly researched and expanded upon since the early nineteenth century, recent studies have increased our understanding of the molecular and cellular basis for the cardiovascular changes occurring in thyroid disease. The hemodynamic changes associated with both hyper- and hypothyroidism have been measured and continue to be an area of research effort. The effects of subclinical stages of thyroid disease on the cardiovascular system and the potential benefits of treatment at this early disease stage are reported with increasing frequency in the literature. This review will address recent progress in defining the mechanism of thyroid hormone action on the heart as well as the hemodynamic changes, clinical consequences, and treatment options associated with both overt and subclinical disorders of thyroid function.

MECHANISMS OF THYROID HORMONE ACTION

The mechanisms of action of triiodothyronine (T3), the more active cellular form of thyroid hormone, include both stimulation of transcriptional processes and cellular membrane activity. Thyroid hormone action is mediated predominately by binding to nuclear receptors and this mechanism has been recently reviewed (1). In brief, thyroxine (T4) and T3 rapidly cross membranes because of their lipophilic nature and possibly through specific transport proteins located in the cell membrane of cardiac myocytes. Thyroid hormone enters the nucleus and binds with high affinity to thyroid hormone receptors. These are activated either as a homodimer or bind a second hormone receptor and become activated as a heterodimer (2,3). These in turn bind to target genes’ thyroid response elements in various configurations leading to transcriptional activity (4–7). The multiple hemodynamic changes reported in hyperthyroidism may be explained by the transcriptional changes of several genes. Thyroid hormone responsive target genes include both regulatory and structural genes. These include transcriptional modulation of
myosin heavy chain alpha, myosin heavy chain beta, making up the thick filament of cardiac myocytes, sarcoplasmic reticulum calcium-ATPase, Na,K-ATPase, phospholamban, voltage gated potassium channels, adenyl cyclase types V and VI, and the Na,Ca-exchanger (8–14). The activation of the myosin heavy chain alpha gene results in an increase in muscle fiber velocity and theoretically in increased myocardial contractility. The dominant component in human myofibril proteins is myosin heavy chain beta, which is repressed (7,8) making the exact contribution of these structural proteins to human cardiovascular manifestations of thyroid disease less certain. Another indirect genomic action of thyroid hormone is the alteration in function of the sarcoplasmic reticulum, including sarcoplasmic reticulum calcium-ATPase and phospholamban. In hyperthyroid heart disease the release of calcium and subsequent reuptake by the sarcoplasmic reticulum, which determines systolic contractile function as well as diastolic relaxation, is altered. This process favors an increase in myocardial contractility (inotropy) and an improvement in diastolic relaxation. Upregulation of sarcoplasmic reticulum calcium-ATPase and changes in the phosphorylation of phospholamban can increase contractility as well as diastolic relaxation and may account for the hemodynamic changes in thyroid disease (10–12).

Although thyroid hormone has a direct effect on the cardiovascular system by modulating the rate of transcription of multiple genes, T3 also exerts an effect on the cellular membrane. Thyroid hormone was first shown to exert a direct effect on myocardial tissue when T4 was incubated with fragments of cardiac tissues from chicken embryos resulting in an increased rate of contraction. Several studies using cardiac muscle, specifically cat papillary muscles, demonstrated an increase in heart rate, isometric tension, and velocity of muscle shortening in the presence of thyroid hormone, in the absence of adrenergic tissue, and in the presence of depletion or blockage of catecholamines (15,16). The rapid increase in cardiac output following an intravenous infusion of T3 supports a direct effect of T3 on cellular membranes (17). Extraneural effects include alterations of various membrane channels and subsequent changes in calcium, sodium, and potassium as mediated through the ATPase system, notably Na,K-ATPase. This increase in concentration leads to short term increases in both inotropy and chronotropy (18–23). The increase in myocyte contractile function in the presence of T3 is due to alterations of multiple cell membrane enzyme systems including a direct effect on myocyte sarcolemmal transduction (20). Not only are there alterations in solute transport (calcium and sodium), but there is also a modulation of mitochondrial respiration, changes in several kinases that may promote signal transduction pathways, and several relevant thyroid hormone binding sites distinct from nuclear binding sites (22). In autoimmune mediated hyperthyroidism, myocardial tissue pathology reveals fibroblast infiltration and degenerative changes. Patients with resulting cardiomyopathy have been found to have antibody receptor binding to thyrotropin stimulating hormone (TSH) receptors in the human heart (4). The results of these studies support a role for a non genomic or direct effect of the thyroid hormone on cardiovascular function. Since several of the membrane channel proteins are upregulated at a nuclear level by thyroid hormone, the boundaries of the genomic and nongenomic actions of thyroid hormone are not clear.

The manifestations of hyperthyroidism resemble an increased adrenergic state. For this reason, an increased sensitivity to adrenergic stimulation in hyperthyroidism has been proposed. Although hyperthyroidism does affect various components of the adrenergic system and a synergistic effect has been reported between thyroid hormone and epinephrine, recent data have not supported the role of an increased sensitivity to catecholamines as the sole cause of the cardiovascular manifestations of hyperthyroidism.
Early studies have suggested an adrenergic contribution secondary to the observation that sympathetic blockade could relieve thyroid storm and alterations in cardiovascular function (24,25). Also, sympatholytic agents, specifically β-adrenergic blockers, have been and continue to be effective in reducing many of the cardiovascular manifestations of hyperthyroidism (26–29). Several mechanisms have been proposed to explain the synergism between catecholamines and thyroid hormone including an increase in the number of adrenergic receptor sites, an increase in the sensitivity of adrenergic receptors, an increase in tissue levels of free catecholamines, and thyroid stimulation of adrenergic nerve terminals (30,31). Recent data has supported a positive or upregulation of β-1-adrenergic receptors in hyperthyroidism while several other components of the adrenergic-receptor complex are negatively or downregulated, so that the net effect on the sensitivity of the heart to adrenergic stimulation in hyperthyroidism remains normal (32–34). Despite an apparent increase in adrenergic activity in hyperthyroid patients, catecholamine concentrations in thyrotoxic patients are normal to low in the serum, and normal rates of epinephrine and norepinephrine secretion by the adrenal have been demonstrated (35–38). Currently, the physiologic basis for the effect of hyperthyroidism on the heart seems to be shifting away from the sympathetic system to the direct cellular mechanisms and transcriptional actions of thyroid hormone. Considerable research is being conducted to further elucidate the contribution of each of the multiple mechanisms by which thyroid hormone exerts its influence on the cardiovascular system.

HYPERTHYROIDISM

Clinical Findings

Classical findings of hyperthyroidism include heat intolerance, irritability, emotional lability, nervousness, muscle weakness, menstrual abnormalities, loss of weight, increased appetite, tremor, hyperactive reflexes, increased sweating, and fatigue (39). The majority of hyperthyroid elderly persons, however, present most frequently with tachycardia, fatigue, and weight loss. In one prospective study, atrial fibrillation and anorexia were the only findings more commonly noted in an elderly population as compared with a younger population (39).

Hemodynamic alterations include an increased resting heart rate, blood volume, left ventricular mass, stroke volume, ejection fraction, and cardiac output. Subsequent clinical manifestations involving the cardiovascular system may include palpitations, tachycardia, elevated systolic blood pressure, decreased peripheral vascular resistance, widened pulse pressure, atrial fibrillation, congestive heart failure (CHF), and angina. These latter problems are more common in the elderly and result from the increase in oxygen demand placed on the aged heart by excessive amounts of the thyroid hormones T4 and T3 and subsequent increased metabolic demands by both the heart and other body organs.

Thyroid Hormone Excess and Cardiovascular Function

Hemodynamic Changes

The pathophysiology of the changes in cardiac function associated with thyroid disease are multifactorial and still under investigation. The associated hemodynamic changes of increased heart rate, blood volume, left ventricular stroke volume, ejection fraction and cardiac output, and decreased systemic vascular resistance have been well defined (5,40). It is currently believed that the high cardiac output state associated with hyperthyroidism...
results from peripheral hemodynamic changes as well as direct changes in myocardial contractility. Cardiac contractility is also increased secondarily because of an increase in peripheral oxygen consumption and metabolic demands associated with excess thyroid hormone.

Tachycardia is frequently associated with hyperthyroidism. Initially, this was felt to be associated with an altered responsiveness to adrenergic input. More recent data support a direct effect of thyroid hormone on pacemaker activity through the sinoatrial (SA) node (41). An increased venous return, secondary to a decreased systemic vascular resistance, activated renin-angiotensin-aldosterone system, and subsequently increased blood volume, contribute to the increase in preload reported in hyperthyroid states (5,6,40,42–44). Although these findings are certainly contributory to the augmented cardiac output associated with hyperthyroidism, cardiac contractility is increased in cardiac myocytes removed from peripheral effects (15,16). Systemic vascular resistance is decreased directly by thyroid hormone’s action on smooth muscle cells as evidenced by invasive measurement after coronary-artery bypass surgery (17). Afterload is reduced in hyperthyroid patients as a result of direct arterial smooth muscle relaxation, which leads to an improvement in stroke volume and subsequently cardiac output. A recent review separated steady and pulsatile components of afterload and hypothesized that pulsatile components of arterial load actually compensate for the reduction in systemic vascular resistance noted in hyperthyroidism. These data cast doubt on the simplified notion of a single factor such as systemic vascular resistance controlling the observed decrease in ventricular afterload in the hyperthyroid patient (40).

Echocardiographic data have become available to further define the cardiac changes in hyperthyroidism. Specifically, it has been demonstrated that diastolic function improves as evidenced by increased isovolumic relaxation and left ventricular filling in hyperthyroid patients (45). These alterations in hemodynamic parameters may explain many of the cardiovascular signs and symptoms of hyperthyroidism and help us better understand many of the cardiac complications associated with hyperthyroidism, including decreased exercise tolerance and increased risk of CHF.

Cardiac Complications
Cardiac complications are the leading cause of death even after successful treatment of hyperthyroidism (46). Electrocardiographic changes commonly associated with hyperthyroidism include repolarization abnormalities, atrial and ventricular extrasystolic beats, sinus tachycardia, and atrial fibrillation. Other electrocardiographic findings include ischemia, left ventricular hypertrophy by voltage criteria, and varying degrees of heart block (47–49). Throughout the literature, there continues to be debate as to whether hyperthyroidism by itself, even without preexisting structural heart disease, can cause the abnormalities frequently seen in the hyperthyroid patient. A recent electrophysiologic study demonstrated that the atrial effective refractory period as well as the atrial conduction delay noted in hyperthyroid patients is arrhythmogenic and could in itself account for the predisposition of hyperthyroid patients to develop atrial fibrillation without prior presence of preexisting structural disease (50). Previous echocardiographic studies, however, have demonstrated that patients with hyperthyroidism and atrial fibrillation are much more likely to have atrial enlargement than those with hyperthyroidism in sinus rhythm (51). Another recent review demonstrated that although most, if not all, of the cardiovascular manifestations associated with hyperthyroidism are reversible with therapy, long-term follow-up reveals an excess cardiovascular and cerebrovascular mortality. This is thought to be most likely due to an increased incidence
of supraventricular dysrhythmias (52). Atrial fibrillation occurs in 5% to 15% of hyperthyroid patients. It is notable that a recent study questioning the usefulness of thyroid function testing in new onset atrial fibrillation found that less than 1% of these patients had hyperthyroidism (53). However, testing is indicated even if the yield is low because multiple studies have shown that treatment of hyperthyroidism may lead to reversion to sinus rhythm; correction of hyperthyroidism is usually recommended before aggressively proceeding with cardioversion for atrial fibrillation (54,55). Although atrial fibrillation secondary to hyperthyroidism is reported to carry a risk of systemic embolism independently of other risk factors for embolization, this risk has not been adequately quantified (14,55).

The hemodynamic changes associated with the hyperthyroid state can uncover previously compensated CHF and coronary artery disease. Exertional dyspnea and CHF can result from hyperthyroidism without underlying structural abnormalities in persons of all age groups (6,14). One possibility is that despite the increase in contractility and other increased hemodynamic parameters in hyperthyroidism, there is an inadequate cardiac reserve to allow a further increase in cardiac function during periods of stress (56). A second possible explanation is that the known cardiac hypertrophy that occurs with hyperthyroidism (as evidenced by an increase in left ventricular mass index) leads to systolic dysfunction. This dysfunction is consistent with hyperthyroid cardiomyopathy and is completely reversible with treatment (57,58). Hyperthyroidism can lead to an acute left ventricular dysfunction that mimics ischemic coronary artery disease. This disorder is rapidly reversible with treatment and is termed “myocardial stunning” because of the reversibility of the disease (59).

The clinical entity of resistance to thyroid hormone may lead to multiple cardiovascular changes that are consistent with hyperthyroidism including increased heart rate, cardiac output, and stroke volume. Cardiac symptoms such as palpitations and signs such as tachycardia and atrial fibrillation were observed less frequently in one series of patients with resistance to thyroid hormone. The authors of that study concluded that this syndrome was associated with an incomplete response to thyroid hormone in the heart (60). While this syndrome is thought to be distinct from other syndromes of thyroid dysfunction, clinical findings may be symptomatically treated with β blockers because of the lower likelihood of developing cardiac complications in this subset of patients.

Subclinical Hyperthyroidism

Definition and Prevalence

Subclinical hyperthyroidism has been defined by the U.S. Preventive Services Task Force and other authorities as a condition associated with a serum TSH concentration below the lower limit of the reference range, usually set at 0.1 mU/L, with normal triiodothyronine and thyroxine values (55,61). It should be noted that subclinical hyperthyroidism has been defined variably in different studies with lower limits for serum TSH values ranging from 0.1 to 0.5 making comparison between studies difficult. Etiology ranges from excessive thyroid hormone replacement therapy to thyroid disease, with the most common cause in the elderly person being long-standing multinodular goiter.

The prevalence of subclinical hyperthyroidism appears to vary with geographic area and dietary iodine intake (62). Individuals with low iodine intake are more commonly affected because of compensatory growth of the thyroid gland in response to low iodine and thus the tendency to develop hyperplastic nodules that may become autonomously functioning thyroid tissue. One study in Italy reported that individuals living in iodine deficient areas had an age-related increase in subclinical hyperthyroidism.
from a prevalence of 0.7% in children to a prevalence of 15.4% in individuals over the age of 75 (63).

In a study of 1210 persons in England, low TSH was found in 6.3% of women and 5.5% of men (64). However, repeat measurements of serum TSH one year later showed a return of TSH to the normal range in the majority of cases. In a study of community residing persons over the age of 85 years, 3% were found to have suppressed TSH (65). Other studies of large populations confirm a similar prevalence of suppressed TSH ranging from 1.8% to 6%, associated with increasing age and female sex (64,66–69).

**Conversion to Overt Hyperthyroidism**

In a U.S. population of 2575 persons over the age of 60 years, 101 were found to have low TSH and, of these, 30 had no history of past or present thyroid disease. Over a four-year follow-up period, most had normal TSH on subsequent testing, but two became overtly hyperthyroid with an increase in serum T4 to above normal values (70). In a prospective study, persons aged 85 years were followed with serum TSH and free T4 until age 89. Of 12 patients with subclinical hyperthyroidism at baseline, 1 became overtly hyperthyroid, 5 had persistent subclinical hyperthyroidism, 5 became euthyroid, and 1 developed subclinical hypothyroidism (65). Several studies suggest that the conversion rate to overt hyperthyroidism ranges from 1.5% to 13% within one year (64,70,71). Thus, the natural history of subclinical hyperthyroidism is variable, sometimes disappearing over time.

**Cardiovascular Alterations**

There are many cardiovascular changes that have been described in subclinical hyperthyroidism. These include increased heart rate, increased prevalence of atrial premature beats, shorter isovolumetric contraction time, shorter prejection period, impaired left ventricular diastolic filling, increased left ventricular mass index, increased mean velocity of circumferential fiber shortening, reduced peak overload, reduced peak oxygen uptake and anaerobic threshold during exercise, increased interventricular septum and left ventricular posterior wall thickness, increased left ventricular end-systolic volume, and impaired left ventricular diastolic filling (Table 1) (72–77). These alterations can lead to reduced exercise performance.

<table>
<thead>
<tr>
<th>Table 1</th>
<th>Cardiovascular Findings Associated with Subclinical Hyperthyroidism</th>
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| Functional alterations | Increased cardiac contractility  
                      | Impaired left ventricular diastolic filling  
                      | Impaired systolic function during exercise  
                      | Increased left ventricular mass index  
                      | Increased intraventricular septal thickness  
                      | Increased left ventricular posterior wall thickness  
                      | Decreased large and small artery elasticity  
                      | Prolonged QTc interval |
| Clinical consequences | Increased heart rate and frequency of atrial premature beats  
                      | Increased incidence of atrial fibrillation  
                      | Lower serum total and LDL cholesterol concentrations  
                      | Reduced exercise capacity  
                      | Increased mortality due to cardiovascular disease |

*Abbreviation: LDL, low-density lipoprotein.*
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Decreased large and small artery elasticity was reported in persons with subclinical hyperthyroidism as compared to controls. These findings were associated with echocardiographic data showing significantly increased left ventricular mass index and interventricular septum thickness (78). Corrected QT intervals, a measure of ventricular repolarization and increased risk of arrhythmia and cardiac mortality, were noted to be significantly longer in patients with subclinical hyperthyroidism (79).

Cardiovascular Disease

Several large studies have been published which have shown an increased risk of atrial fibrillation in patients with subclinical hyperthyroidism. One recent retrospective study reported that the risk of atrial fibrillation was five times more likely in patients with subclinical hyperthyroidism, similar to that found in patients with overt hyperthyroidism (57,58,71,80–82). In a prospective study of 3233 community-residing persons over the age of 65 years, 1.5% were found to have subclinical hyperthyroidism at baseline. Over the course of 13 years of follow-up, those with subclinical hyperthyroidism had twice the risk of developing atrial fibrillation than those with baseline euthyroidism (83). An increase in the number of cardiac L-type Ca\(^{2+}\) channels by up to threefold has been reported in patients who are subclinically hyperthyroid, a probable mechanism for the increased rate of atrial fibrillation (84).

There are conflicting reports regarding the impact of subclinical hyperthyroidism on mortality. One study reported an increase in all-cause and cardiovascular mortality in individuals over the age of 60 with subclinical hyperthyroidism with serum TSH concentrations lower than 0.5 mIU/L (85). Another report of elderly persons with untreated subclinical hyperthyroidism who were followed from age 85 through 89 years has demonstrated an increase in both cardiovascular and all-cause mortality (65). However, several recent studies have shown no association between subclinical hyperthyroidism and risk of coronary heart disease (CHD) events or death (69,83).

Management of Hyperthyroid Associated Cardiac Disease

Cardiac findings such as palpitations, sinus tachycardia, and even tachyarrhythmias appear to be well tolerated in most hyperthyroid people, rarely produce an immediate crisis and in most cases are amenable to conservative treatment pending correction of the hyperthyroid state itself. While radioactive iodine is an excellent treatment for the underlying hyperthyroid state, especially in the elderly patient, the time to onset of action can be weeks to months. If an immediate effect is needed, Lugol’s solution may be administered after an initial dose of antithyroid medication such as propylthiouracil or methimazole. Iodine rapidly reduces circulating levels of thyroid hormone by blocking essential steps in thyroid hormone production. However, propylthiouracil or methimazole must be used in conjunction with the iodine to inhibit thyroid hormone synthesis, and to prevent the possibility of a thyroid nodule or diffuse toxic goiter from converting the iodine to thyroid hormone and effectively worsening the hyperthyroid state (6,14).

In patients who are unstable with signs of cardiac compromise, intravenous \(\beta\) blockers rapidly decrease heart rate and may reduce the conversion of T4 to T3 by approximately 15%. If the patient presents with CHF, diuretics are still the mainstay of treatment. Digoxin is of use in patients with hyperthyroid mediated CHF, although there may be a Na,K-ATPase mediated resistance to its action (6).
Treatment of atrial fibrillation should be tailored to correcting the hyperthyroidism because of the high rate of spontaneous cardioversion once thyroid hormone concentrations are normalized (54). Most of these conversions take place within three weeks of becoming euthyroid and no spontaneous conversions occur if atrial fibrillation is still present after four months of euthyroidism or if atrial fibrillation was present for more than 13 months before becoming euthyroid. Patients who remain in atrial fibrillation beyond 16 weeks of return to the euthyroid state are candidates for cardioversion.

The decision to anticoagulate has not been elucidated in the case of hyperthyroid associated atrial fibrillation in any randomized controlled trials. However, it has been recommended that older patients with comorbid hypertension, CHF, left atrial enlargement or left ventricular dysfunction or with other conditions increasing the risk of systemic embolization, or those patients with longer duration of atrial fibrillation (14,15,86). Hyperthyroidism increases the sensitivity to the anticoagulant effect of warfarin, resulting in a greater lowering of coagulation factors II and VII and greater increase in prothrombin ratio and partial thromboplastin time (87). When warfarin is used, the dose should keep the international normalization ratio (INR), between 2.0 and 3.0, and continued until euthyroidism has been restored and there is a return to normal sinus rhythm (88). Individual case-by-case review of pertinent risk factors for embolization is appropriate before making the decision to initiate anticoagulant.

Management of Subclinical Hyperthyroidism

Treatment at this early stage of hyperthyroidism is controversial secondary to the low rates of progression to overt hyperthyroidism. A recent long-term study of patients with untreated subclinical hyperthyroidism demonstrated an increase in both cardiovascular and all-cause mortality (89). When these data are coupled with the findings of diminished self-reported ratings of quality of life and a higher rate of osteopenia in persons with subclinical hyperthyroidism, it is reasonable to consider earlier, more aggressive treatment, especially in individuals who already manifest these changes (55,90).

While there have been no randomized prospective trials evaluating the treatment of subclinical hyperthyroidism, there is a consensus that the therapy should be initiated in elderly individuals and in younger persons with heart disease or evidence of other problems, such as bone loss, that may be impacted by this entity and who have serum TSH levels less than 0.1 mU/L. A consensus panel of endocrinologists has recommended treatment for those with complete TSH suppression of less than 0.1 mU/L but recommends periodic retesting of thyroid function in patients with partial TSH suppression of 0.1 to 0.4 mU/L (Table 2) (91,92). It has been suggested that all postmenopausal women, individuals over age 60, and those with a history of heart disease, osteoporosis, or symptoms be treated if the TSH is less than 0.1 mU/L and that a similar approach be considered if the TSH is between 0.1 and 4 mU/L in this same population. Premenopausal women or those less than 60 years of age without a history of heart disease, osteoporosis, or symptoms but who have a TSH less than 0.1 mU/L are suggested to have a radioiodine uptake and scan and bone density study, but therapy remains optional as there is little clinical evidence for significant benefit in these patients. Similar individuals with TSH levels between 0.1 and 0.4 mU/L should have no therapy though one might want to consider a radioiodine uptake and scan and follow-up periodic TSH testing (93,94). Treatment leading to the return of serum TSH to normal was associated with significant improvement in cardiovascular function including a decrease in the heart rate, total number
of beats during 24 hours, number of atrial and ventricular premature beats, reduction in left ventricular mass index, interventricular septum thickness, and left ventricular posterior wall thickness at diastole (95).

Although treatment at this early stage of hyperthyroidism is controversial because of the low rates of progression to overt hyperthyroidism, subclinical hyperthyroidism can be associated with clinical findings significant enough to make treatment necessary in select populations as stated above. Findings of diminished self-reported ratings of quality of life in persons with subclinical hyperthyroidism have led some authorities to recommend early, more aggressive treatment (56,90).

HYPOTHYROIDISM

Hypothyroidism, defined as an elevated serum TSH along with serum T4 or free T4 below the lower limit of normal, is relatively common in the general population with a well-established relationship to gender and age. The incidence of hypothyroidism in women is three to four times that in men, and there is a clear increase in prevalence with advancing age so that it is found in 15% to 20% of women over the age of 75 and 4% to 7% of elderly men. The American Thyroid Association now recommends that all persons over the age of 50 have annual screening for thyroid hormone abnormalities after studies have shown the cost-benefit from such practice (96).

Cardiovascular manifestations of hypothyroidism occur as a consequence both of the effects of thyroid hormone deficiency on the myocardium and of hypothyroid-associated dyslipidemia on arterial vasculature. Histologically, swelling of the myofibrillar elements, interstitial fibrosis, basophilic degeneration, and tissue edema

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**Table 2  Treatment Recommendations for Subclinical Thyroid Disease**

<table>
<thead>
<tr>
<th>Subclinical hyperthyroidism</th>
<th>Normalization of thyroid function with antithyroid drugs or ¹³¹I for patients with:</th>
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<tr>
<td></td>
<td>Clinical features of hyperthyroidism</td>
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<tr>
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<td>Atrial fibrillation</td>
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<td>Ischemic heart disease</td>
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<td>Osteopenia/osteoporosis</td>
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<td>Suppressed TSH &lt;0.1 mU/L</td>
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<td></td>
<td>Development of increase in T₄, free T₄, or T₃ during follow-up</td>
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<td></td>
<td>Monitor TSH/free T₄ at 6- to 12-month intervals in asymptomatic patients with TSH 0.1-0.4 mU/L</td>
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<tr>
<th>Subclinical hypothyroidism</th>
<th>T₄ replacement for patients with:</th>
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<tbody>
<tr>
<td></td>
<td>Serum TSH &gt;10 mU/L,</td>
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<tr>
<td></td>
<td>Serum TSH 5–10 mU/L, and positive antimicrosomal antibodies or symptoms of mild hypothyroidism</td>
</tr>
<tr>
<td></td>
<td>Monitor TSH/free T₄ at 6- to 12-month intervals for patients with serum TSH 5–10 mU/L and negative antimicrosomal antibodies and no evident symptoms of hypothyroidism</td>
</tr>
</tbody>
</table>

**Abbreviations:** T₄, thyroxine; TSH, thyroid-stimulating hormone; T₃, triiodothyronine.
have been described (97). There appears to be deposition of mucopolysaccharide, likely reflecting the decline in certain enzymes necessary for the breakdown of these substances. Electron microscopic studies reveal thickening of the capillary basement membrane similar to that observed in diabetes mellitus and in persons of advanced age (98,99). Numerous other ultrastructural changes have been described, including loss of mitochondrial cristae.

At the organ level, the heart in persons with hypothyroidism may be dilated, pale, and flabby as a result of myxedematous infiltration, but there is no evidence of hypertrophy (100). Pericardial effusion may be present.

**Thyroid Hormone Deficiency and Cardiovascular Function**

Perhaps the most widely accepted change noted in the setting of hypothyroidism is a reduction in myocardial contractility. Using isolated right ventricular papillary muscles from hypothyroid cats and dogs, a decrease was noted in isometric tension and the rate of tension development. The time taken to reach peak tension increased at all muscle lengths and isotonic force-velocity relations shifted downward and to the left, supporting a depressed contractile state (101,102). In all animal studies reported, CHF was not noted despite significant reductions in circulating levels of thyroid hormone. It has been postulated that decreased myocardial contractility in hypothyroidism may result from a reduction in the thyroid-adrenergic relationship, with either a diminished response to a given amount of catecholamine or a reduced amount of free catecholamine available to interact at the cardiac receptor site. Studies have reported an increase, decrease, and no change in cardiovascular sensitivity to catecholamine stimulation in the setting of hypothyroidism (103–106). Levels of norepinephrine in myocardial tissue of hypothyroid cats were not reported to be affected by thyroid status (101), and thus it appears unlikely that a lower level of catecholamine exposure to the cardiac receptor is the cause of significant cardiac effects. Studies have shown a reduction in β-adrenergic receptor activity in atria from hypothyroid rats and an increase in α-receptor activity in the same tissue (107). This reduction in the number and/or affinity of β receptors in cardiac tissue could result in a depressed myocardial response. Because contractile function is depressed in isolated papillary muscles from hypothyroid rats (101), thyroid hormone deficiency seems to have a direct effect and is responsible for at least a component of the cardiovascular change induced by the hypothyroid state.

The rate of calcium uptake and calcium-dependent ATP hydrolysis by isolated cardiac myocytes is reduced in the setting of hypothyroidism and may be a mechanism for decreased myocardial contractility (108). A reduction in myocyte calcium ATPase activity of the sarcoplasmic reticulum has been described in both rat and mouse models of hypothyroidism (109–111), although not in a rabbit model (111).

The bradycardia that often occurs in hypothyroidism is thought to result from the lack of thyroid stimulation of SA node cells (112), further impacted by a reduction in sympathoadrenal stimulation. A decreased rate of diastolic repolarization and prolonged action potential duration has also been described.

The hemodynamic changes seen in hypothyroidism are opposite to those seen in hyperthyroidism and are less likely to be associated with overt clinical findings. Systemic vascular resistance is increased, heart rate is decreased, isovolumic relaxation time is increased, and there is a decrease in the ejection fraction, blood volume, and cardiac output (14,45,111). An increase in systemic vascular resistance, decrease in heart rate, and decrease in the renin-angiotensin-aldosterone system combined with a slowed diastolic relaxation lead to a decrease in preload and subsequent decrease in stroke volume. Thus, the
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functional consequence of decreased ventricular contractility, ventricular filling, and stroke
volume is reduced cardiac output. The increase in systemic vascular resistance can lead to
diastolic hypertension and contribute to an increased risk for adverse cardiovascular events.

Changes in blood lipoprotein composition in hypothyroidism have implications for
atherogenesis. Short-term hypothyroidism is associated with an increase in plasma
lipoprotein (a) and T3 therapy rapidly lowered lipoprotein (a) together with apolipoprotein
B and low-density lipoprotein (LDL) cholesterol. These findings support the hypothesis
that thyroid hormone is capable of regulating plasma lipoprotein (a) and apolipoprotein B
in a parallel manner. Elevated concentrations of lipoprotein (a) in combination with LDL
cholesterol may be involved in the increased risk of cardiovascular disease which is
associated with hypothyroidism (113). Changes in LDL receptor activity are significantly
correlated with changes in LDL cholesterol, but not with changes in lipoprotein (a). The
LDL receptor pathway appears to be involved in the catabolism of lipoprotein (a) to a
limited extent (114). Hypothyroidism has been associated with elevated levels of total and
high-density lipoprotein (HDL) cholesterol, total/HDL cholesterol ratio, apolipoprotein AI,
and apolipoprotein E. The increase in apolipoprotein AI without a concomitant increase in
apolipoprotein AI suggests a selective elevation of HDL2. These effects were found to be
reversible with treatment of the hypothyroidism (115).

Pulse wave analysis from recordings at the radial artery in patients with
hypothyroidism demonstrates increased augmentation of central aortic pressures and
central arterial stiffness. These alterations lead to hypertension and increased cardiac
afterload and, along with hypothyroid-associated endothelial dysfunction, contribute to
increased cardiovascular risk. These abnormalities are reversed by appropriate thyroid
hormone replacement (116).

Other cardiovascular risk factors for patients with hypothyroidism include smoking,
elevated levels of homocysteine, elevated C-reactive protein, coagulation abnormalities,
and insulin resistance (117).

Clinical Cardiac Manifestations of Hypothyroidism

Clinically evident cardiac manifestations of hypothyroidism occur only in association
with a significant reduction in the levels of circulating thyroid hormone. Studies using
oxygen consumption as a corollary of thyroid hormone status have reported few cardiac
symptoms in otherwise healthy persons until oxygen requirements decline by 75%. This
level is highly variable, however. Many persons with hypothyroidism have coexisting
medical conditions that compromise the cardiovascular system and may lower the
threshold for cardiac problems. The reduced requirement for oxygen by the hypothyroid
myocardium may be protective against angina. In fact, angina may develop only after
therapy with thyroid hormone has been initiated.

Symptoms due to the effect of hypothyroidism on the heart include dyspnea on
exertion and easy fatigability. Less frequent are complaints of orthopnea, paroxysmal
nocturnal dyspnea, and angina. Physical findings often present in patients with
hypothyroidism include bradycardia, narrowed pulse pressure, mild hypertension, distant
heart sounds, and evidence of cardiomegaly. Reduced cardiac output with resultant
decrease in glomerular filtration rate can lead to renal sodium retention and peripheral
edema in the absence of CHF. In general, there is no change in the jugular venous pressure.
In patients with severely diminished thyroid function, however, infiltrative cardiomyop-
athy, evidence of peripheral edema or nonpitting edema of the lower extremities, pleural
effusion, and even ascites may be noted and can produce a clinical picture suggesting CHF.
The presence of nonpitting edema raises the possibility that hypothyroidism is present.
The electrocardiogram may be normal in the presence of hypothyroidism but more often there is bradycardia, prolonged QT interval, flattening or inversion of the T wave, particularly in lead II, and low-amplitude P, QRS complex, and T waves (118). These findings may result from a direct effect of thyroid hormone deficiency, but can also be the result of a pericardial effusion that may accompany hypothyroidism. Although not common, incomplete and complete right bundle branch block occur with greater frequency (119). Ventricular arrhythmias may be seen including the ventricular tachycardia of the syndrome of torsades de pointes. With replacement therapy, these changes return to normal and may even precede the return to normal of other clinical features of the disease. The echocardiogram in hypothyroidism demonstrates features of decreased left ventricular contractility with increased systolic time interval and prolongation of isovolumic relaxation time. Small pericardial effusions may be present in as many as 50% of hypothyroid patients but do not affect cardiac function (120,121).

Studies suggest that in the absence of other coexisting diseases, CHF is an extremely uncommon finding in hypothyroidism (122). In the setting of shortness of breath, pleural effusions, cardiomegaly, and other symptoms, it is often difficult to distinguish CHF from what has been termed myxedema heart, a cardiomyopathy resulting from insufficient quantities of thyroid hormone that is reversible with thyroid hormone replacement.

The absence of pulmonary congestion, diminished plasma volume, high protein content of pleural or pericardial effusions, and normal resting venous, atrial, pulmonary artery, and right ventricular end-diastolic pressures are highly suggestive of myxedema. Exercise results in an increase in cardiac output and ejection fraction in persons with myxedema, in contrast to the impaired response in those with congestive failure (123,124). The hemodynamic changes associated with hypothyroidism appear to respond to thyroid hormone, but they are not very responsive to diuretic and digoxin therapy. Since in many persons both conditions occur together, there is a great deal of variability in clinical response.

An increase in the risk for CHD has been associated with hypothyroidism (117). Decreased measures of thyroid function and serum HDL have been observed to be more common in patients with coronary artery disease (125). Treatment of hypothyroidism with hormone replacement has been observed to protect against the angiographic progression of coronary artery disease, perhaps due to metabolic effects of thyroid hormone on plaque progression (126).

Subclinical Hypothyroidism

Definition and Prevalence

Large population surveys have identified a significant proportion of individuals who have serum TSH levels above the accepted upper limit of normal but in whom serum concentrations of total and free T4 as well as total and free T3 are normal and overt symptoms of hypothyroidism are usually mild or absent. This syndrome, which has been termed subclinical hypothyroidism, is most commonly found in women above the age of 60 and has been observed in 15% to 20% of women over the age of 75 (127–132). Antithyroid antibodies are often present, suggesting an autoimmune etiology (130,131,133). It is thought that the failing thyroid gland responds with an increase in TSH secretion which, in turn, is capable of further driving the thyroid to maintain normal levels of T4 and T3 until true thyroid failure ensues.

In the Framingham study, 5.9% of subjects over the age of 60 had clearly elevated serum TSH concentrations (>10 mU/L) with normal serum T4 levels and an additional 14.4% had slightly elevated serum TSH (5–10 mU/L) with normal serum T4 (134).
Thyroid Heart Disease in the Elderly

A thyroid screening survey of 1149 community-residing women with mean age of 69 ± 7.5 years identified 10.8% as having subclinical hypothyroidism (127). Other studies have established a prevalence rate of between 25 and 104 per 1000 persons with the highest rate occurring in women over age 55 years. The incidence in women aged between 40 and 60 years may be as high as 10%.

Data from the Whickham study indicate that 60% of subjects with serum TSH values greater than 6 mU/L and 80% of those with TSH values greater than 10 mU/L had demonstrable antithyroid antibodies in their serum. Of the entire population of women, 5% had both elevated TSH levels and antithyroid antibodies (135).

Progression to Overt Hypothyroidism

One question of clinical importance is what is the likelihood that persons with laboratory criteria for subclinical hypothyroidism will go on to develop clinical hypothyroidism. In a long-term follow-up study, women who initially had antithyroglobulin and antimicrosomal antibodies along with a serum TSH of greater than 6 mU/L developed overt hypothyroidism at the rate of 5% per year. No cases developed in women with borderline elevation of TSH only (6–10 mU/L) and only one case developed in the 67 women who had antithyroid antibodies with normal TSH levels (130).

Other studies support progression to overt hypothyroidism at the rate of 7% per year in women with elevated serum TSH and high titers of antithyroid antibodies with ranges from 1% to 20% per year (133,136). There is a relationship between the degree of elevation of TSH and the long-term risk of progression to overt hypothyroidism with an initial TSH greater than 12 mU/L resulting in 77% incidence of overt hypothyroidism by 10 years of follow-up (137,138). The presence of antithyroid antibodies indicates underlying chronic autoimmune thyroiditis and constitutes a significant risk factor for the development of clinically apparent hypothyroidism in women who are found to have isolated elevated values of serum TSH (137,138).

Cardiovascular Alterations

There is evidence that systolic contractility on effort and left ventricular diastolic contractility at rest are decreased in patients with subclinical hypothyroidism (Table 3) (72). These changes may have little functional significance in the resting state but symptoms can develop during cardiopulmonary exercise. The altered contractility and clinical response to exercise are corrected with thyroid hormone treatment (139–141). Although subclinical hypothyroidism has been associated with a prolongation of the QT interval, little has been reported regarding its clinical consequences.

As in patients with overt hypothyroidism, those with subclinical hypothyroidism have been shown to have alterations in peripheral vasculature. Both diastolic blood pressure and pulse wave velocity were significantly increased in patients with subclinical hypothyroidism compared with euthyroid persons (142). Pulse wave analysis has also demonstrated increased arterial stiffness in patients with subclinical hypothyroidism, which improved after thyroid hormone treatment (143).

There have been many reports indicating that subclinical hypothyroidism is associated with alterations in circulating concentrations of lipids that may enhance the risk for development of vascular disease (141–148). A recent study of 2108 community-residing persons demonstrated that in the 119-person subgroup (5.6%) with subclinical hypothyroidism there was a significant increase in total serum cholesterol and in LDL cholesterol with no change in HDL cholesterol (149).
Cardiovascular Disease

The relationship between subclinical hypothyroidism and cardiovascular disease has been the subject of many clinical studies that have yielded conflicting results. A study of 1922 patients indicated that subclinical hypothyroidism was not associated with an adverse cardiovascular risk profile (150). This observation was further supported by data from several large longitudinal studies of community-residing persons (83,151).

However, a number of recent studies suggest that subclinical hypothyroidism is a risk factor for cardiovascular disease. The relationship between subclinical hypothyroidism and/or autoimmune thyroid disease and CHD was evaluated in a Japanese population. Ninety-seven patients diagnosed as having CHD by a coronary angiogram (CHD group) and 103 healthy subjects matched for age, sex, and body mass index (control group) were included in the study. Thyroid function, thyroid autoantibodies, and serum lipid concentrations were measured in the CHD and control groups. The CHD group exhibited significantly decreased levels of serum free T3 and free T4 and significantly increased serum TSH levels as compared with the control group, indicating a significant decrease in thyroid function in the CHD patients. Serum HDL cholesterol levels were significantly decreased in the CHD group (125). Another Japanese study of 2550 men and women with mean age of 58.5 years found 10.2% to have subclinical hypothyroidism (mean age 62 years). Men with subclinical hypothyroidism had a prevalence of ischemic heart disease four times greater than euthyroid men but no increase in intracranial hemorrhage or cerebral infarction. Over 12 years of follow-up, there was a significant increase in all-cause mortality in the subclinical hypothyroid men but not in women (152). A longitudinal study of 2108 men and women with a mean age of 50 years found a significant increase in prevalence of CHD in both men and women with

### Table 3  Cardiovascular Findings Associated with Subclinical Hypothyroidism

<table>
<thead>
<tr>
<th>Category</th>
<th>Findings</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ventricular function</td>
<td>Impaired systolic function on effort</td>
</tr>
<tr>
<td></td>
<td>Impaired left ventricular diastolic function</td>
</tr>
<tr>
<td></td>
<td>at rest/delayed relaxation time</td>
</tr>
<tr>
<td></td>
<td>Right ventricular systolic and diastolic</td>
</tr>
<tr>
<td></td>
<td>dysfunction</td>
</tr>
<tr>
<td></td>
<td>Increased risk of CHF</td>
</tr>
<tr>
<td>Peripheral vasculature</td>
<td>Increased systemic vascular resistance</td>
</tr>
<tr>
<td></td>
<td>Impaired vasodilation</td>
</tr>
<tr>
<td></td>
<td>Increased carotid artery intima-media thickness</td>
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<tr>
<td></td>
<td>Increased arterial stiffness</td>
</tr>
<tr>
<td></td>
<td>Increased pulse-wave velocity</td>
</tr>
<tr>
<td></td>
<td>Increased diastolic blood pressure</td>
</tr>
<tr>
<td></td>
<td>Increased peripheral vascular disease</td>
</tr>
<tr>
<td>Dyslipidemia</td>
<td>Increased total cholesterol</td>
</tr>
<tr>
<td></td>
<td>Increased LDL cholesterol</td>
</tr>
<tr>
<td></td>
<td>Increased apolipoprotein B</td>
</tr>
<tr>
<td></td>
<td>Increased lipoprotein (a)</td>
</tr>
<tr>
<td>Atherosclerosis</td>
<td>Increased ischemic/coronary heart disease</td>
</tr>
<tr>
<td></td>
<td>Increased risk of myocardial infarction</td>
</tr>
<tr>
<td></td>
<td>Increased aortic atherosclerosis</td>
</tr>
<tr>
<td>Coagulation</td>
<td>Increased factor VII activity</td>
</tr>
<tr>
<td>Mortality</td>
<td>Increased cardiac mortality</td>
</tr>
<tr>
<td></td>
<td>Increased all-cause mortality</td>
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</tbody>
</table>

**Abbreviations:** CHF, congestive heart failure; LDL, low-density lipoprotein.
subclinical hypothyroidism who had a TSH level greater than 10 mU/L (69). Similarly, a study of 2730 men and women aged 70 to 79 years who were followed for a period of four years revealed an increased risk for CHF in persons with subclinical hypothyroidism who had TSH levels of 7 mU/L or greater (153). In this population, subclinical hypothyroidism was not associated with an increased risk of CHD, stroke, peripheral arterial disease, or cardiovascular-related or total mortality.

Among elderly residents of a nursing home, 6% were found to have subclinical hypothyroidism, and, of these, 83% had dyslipidemia and 56% had evidence of coronary artery disease in contrast to a 16% incidence of coronary artery disease in euthyroid residents (154).

Women with hypercholesterolemia have an increased likelihood of having coexisting subclinical hypothyroidism (155). Patients with subclinical hypothyroidism have been found to have a relative increase in LDL cholesterol and decrease in HDL cholesterol with a corresponding higher prevalence of ischemic heart disease (144). In a large group of elderly women with evidence of aortic atherosclerosis, 13.9% were found to have subclinical hypothyroidism and in those women with a history of myocardial infarction, 21.5% had subclinical hypothyroidism (127). The presence of subclinical hypothyroidism was accompanied by a high prevalence of both aortic atherosclerosis and myocardial infarction, with an even higher prevalence in those who also had detectable thyroid antimicrosomal antibodies. A higher rate of adverse events, including reocclusion, has been observed after percutaneous coronary intervention in patients with subclinical hypothyroidism (145). An increase in factor VII activity has been found in a study of patients with subclinical hypothyroidism, raising the possibility of a hypercoagulable state that may lead to an increased risk of thromboembolism (156).

Peripheral vascular disease is also increased in persons with subclinical hypothyroidism. Carotid artery intima-media thickness, a recognized risk factor for cardiovascular disease, was assessed in patients with subclinical hypothyroidism by high-resolution ultrasonography and found to be increased and positively related to age, TSH, and LDL cholesterol levels. Treatment with thyroid hormone reduced total and LDL cholesterol and carotid-intima thickness (157). In a nursing home population of mean age 79 ± 9 years, 78% of persons identified with subclinical hypothyroidism were found to have symptomatic peripheral vascular disease (158).

Effects of Thyroid Hormone Treatment

Treatment with L-thyroxine has resulted in improved systolic and diastolic function, improvement in left ventricular ejection fraction with exercise and decrease in systemic vascular resistance (72,142,159). The treatment has also resulted in decrease in total and LDL cholesterol, increase in serum HDL, and decrease in LDL and apolipoprotein b (141,144,145,157). A meta-analysis has further demonstrated a modest but effective reduction in total and LDL cholesterol in treated cases of subclinical hypothyroidism (148). There are no substantive data as yet to indicate that early treatment of subclinical hypothyroidism with thyroid hormone replacement will be effective in reducing the risk for subsequent development of atherosclerosis or coronary artery disease.

Myxedema Coma

Myxedema coma is an extreme, life threatening form of hypothyroidism that occurs almost exclusively in the elderly, usually in association with infection, severe trauma, cold exposure, or following administration of sedatives, tranquilizers or narcotics. Cardiac
manifestations include bradycardia, hypotension, and shock. The electrocardiogram, in addition to bradycardia, will usually show low voltage and T wave flattening. Serum CK is often markedly elevated and the clinical picture may resemble that of a myocardial infarction.

Management of Overt Hypothyroidism

Younger persons or those with no evidence of cardiovascular compromise may be started on L-thyroxine in an initial dose of 25 µg daily. Because so many elderly persons with hypothyroidism may have underlying cardiovascular abnormalities, initiation of thyroid hormone replacement therapy in this population should be with a smaller dose of L-thyroxine, i.e. 12.5 µg daily. The use of diuretic therapy and digoxin should be reserved for persons in whom there is clear evidence of coexisting CHF. The starting dose should be increased by 12.5 to 25 µg increments at four to six week intervals, realizing that both age and hypothyroidism prolong the half-life of L-thyroxine. Because it takes approximately five half-lives to reach a steady state, laboratory monitoring of serum TSH is necessary to avoid too rapid a rise in dosing. Dose adjustments are made until the level of serum TSH has declined to within the normal range or the patient develops signs of toxicity. In general, elderly persons who are hypothyroid require a replacement dose of between 75 and 100 µg daily compared to an approximate dose of 100 to 125 µg for younger persons. L-thyroxine is the preferred thyroid hormone for replacement because T3 exerts a “burst” effect on the myocardium and is less well tolerated. It also has a shorter half-life, thereby having a less equilibrated metabolic profile. Combination therapies also share the disadvantage of T3, a component in all these medications.

In individuals who have severe ischemic cardiac disease, it may be difficult to return the patient to the euthyroid state without provoking cardiac symptoms. However, in a study of hypothyroid patients who had known symptomatic coronary artery disease, treatment resulted in either no change or an improvement in symptoms in 84% of the patients with only 16% exhibiting an increase in symptoms (160). Attempt should be made to maximize the antianginal regimen, including administration of β blockers, vasodilators, and calcium channel blockers. If this approach fails, the patient should undergo evaluation for the possibility of angioplasty or coronary artery bypass surgery (117,161).

The patient with myxedema coma should be cared for in an intensive-care unit setting and treatment started promptly with an initial dose of 300 to 500 µg of L-thyroxine given intravenously. Once there is evidence of a clinical response such as rise in body temperature and heart rate, the daily dose of L-thyroxine should be reduced to 25 to 50 µg orally and slowly further adjusted by monitoring the serum TSH (162,163).

Management of Subclinical Hypothyroidism

There have been several recent publications dealing with the issue of treatment for subclinical thyroid dysfunction (91,92,94,164,165). Considerable controversy, however, remains. Two reports on subclinical thyroid disease were prepared by a panel of experts appointed by the American Association of Clinical Endocrinologists, the American Thyroid Association, and The Endocrine Society who carried out an exhaustive review of the literature using principles of evidence-based medicine. These reports addressed issues of screening, evaluation, and management of patients with subclinical thyroid disease and culminated in a consensus statement of conclusions and recommendations prepared by the panel members, which was published in 2004 (91,94). Subsequently, a response document from representatives of three organizations was prepared and published in 2005, pointing
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out areas where there was disagreement with the consensus conference recommendations (92). A rebuttal by the chair of the consensus panel and an editorial have also been published (164,165).

The consensus panel concluded that routine treatment of patients with subclinical hypothyroidism with serum TSH levels of 4.5 to 10 mU/L was not warranted but indicated that treatment is reasonable for patients with TSH levels greater than 10 mU/L. This recommendation was based on data from patients with TSH above 10 mU/L regarding the projected rate of progression from subclinical to overt hypothyroidism and the effects of thyroxine treatment on symptoms, depression, lipid profiles, and cardiac function (91).

The response of the three sponsoring societies to the consensus panel disagrees with some of the panel’s conclusions. Thus, the three societies recommend routine screening for subclinical thyroid disease according to previously published guidelines. Further, they recommend routine treatment of patients with subclinical hypothyroidism who have TSH levels between 4.5 and 10 mU/L (92).

At present, a conservative approach is to monitor patients identified with the syndrome with serum TSH and free T4 at 6 to 12 month intervals. Replacement therapy with thyroxine should be given to those patients with serum TSH greater than 10 mU/L and to those with TSH between 5 and 10 mU/L, who have either high levels of antimicrosomal antibodies or symptoms consistent with mild hypothyroidism (Table 2).

CONCLUSIONS

Thyroid hormone has multiple effects on the cardiovascular system, acting through a variety of mechanisms. Clinically, these effects are manifest in patients with hyperthyroidism and hypothyroidism, both in the overt forms of the diseases and in the now well-recognized subclinical forms. Treatment aimed at restoration of thyroid function to normal is effective in correcting many of the alterations in cardiovascular function and the clinical expressions which are the consequence of thyroid dysfunction. Evidence continues to accumulate on whether or not there are benefits of treatment of the subclinical stages of thyroid disease, especially subclinical hypothyroidism.

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Heart Failure

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EPIDEMIOLOGY AND RISK FACTORS

Perhaps no disorder, cardiac or otherwise, is more associated with the elderly than the heart failure (HF) syndrome. Over 80% of HF patients are aged 65 years or older. HF represents the most frequent reason for hospitalization in Medicare beneficiaries, consuming $4 billion in this population in 2001 (1). Over the past three decades, in the United States and other western countries, the prevalence and incidence of HF have increased steadily over this period (2). Between 1979 and 1999, hospital discharges for HF in the United States nearly tripled in women and more than doubled in men (2). The national prevalence of HF is approximately 5 million, and approximately 550,000 new cases occur annually.

Both the prevalence and incidence of HF increase markedly with age. In the Framingham Heart Study, the incidence of HF doubled with successive decades from 0.8% in those younger than 50 years to 9.1% among those 80 to 89 years old (3). In the Cardiovascular Health Study (CHS), a population-based observational study of cardiovascular (CV) risk conducted in four U.S. communities among persons who were aged 65 years or older, HF prevalence increased in women from 4.1% at age 70 to 14.3% at age 85 (Fig. 1); HF prevalence was higher in men but with a similar age trend (7.8% increasing to 18.4%) (4). In the community-based Rochester Community Project, the mean age of patients who developed new HF, in Olmstead County, Minnesota, U.S.A., was 76 years, and nearly 50% were older than 80 years (5).

Among CHS participants, HF incidence was greater in men than in women. In the Framingham Heart Study, although men are substantially more likely than women to develop HF before age 65, the ratio of men to women approached unity after this age (6). In the Framingham Study, HF incidence declined by 31–40% in women but remained unchanged in men from 1950–1969 to the 1990s (7). The prevalence and incidence of HF were similar in African-Americans and whites in CHS (4,6).
Major factors in the increasing prevalence and incidence of HF are the growing proportion of elderly Americans, and chronic hypertension and coronary heart disease (CHD), the two most common antecedent conditions. In addition to age, several common risk factors for HF have been identified in older populations. Over 75% of HF patients have antecedent hypertension. Studies in older populations have found that pulse pressure, an index of arterial stiffness, is the strongest blood pressure predictor of HF (8,9). CHD, especially prior myocardial infarction, and degenerative aortic valvular disease are potent predictors of HF in the elderly. Male sex, obesity, and diabetes were independently predictive of HF in CHS (6) and the New Haven cohort of the Established Population for Epidemiological Studies of the Elderly (EPESE) (9). Additional predictors of HF in CHS were prior stroke, atrial fibrillation, renal dysfunction, reduced ankle-arm index, increased C-reactive protein, left ventricular hypertrophy (LVH), and reduced forced expiratory volume (6).

Bertoni et al. performed a study utilizing a 5% sample of the Medicare database over a five-year period. Their findings indicated that among older patients, the presence of diabetes not only substantially increased the five-year incidence of HF but also markedly increased the mortality risk (10).

Obesity has been relatively underrecognized as a modifiable risk factor for HF. In fact, every major population study in the United States that has been assessed has found obesity to be a potent and independent risk factor for HF, particularly among the elderly. A recent report from the Health, Aging, and Body Composition (HABC) study by Nicklas et al. (11) not only confirmed this increasingly important link, but also quantitatively assessed the risk of differing patterns of body composition. The authors identified central obesity as the pattern most strongly associated with the development of HF in older persons (11). It is likely that there is an interaction between obesity and chronic inflammation biomarkers as risk factors for HF. Among a variety of adverse consequences for HF, adiposity contributes to alterations in diastolic function and LV mass (12). Furthermore, caloric restriction appears to reduce the age-related decline in diastolic function (13).

On the basis of a volume of reports over the past two and a half decades, it is now well established that a substantial proportion of HF patients, mostly elderly, have an HF with a normal ejection fraction (HFNEF). Reports from population-based studies such as...
Framingham (3), CHS (4), Olmsted County (5), and the Strong Heart Study of American-Indians (14) all suggest that at least half of all elderly HF patients have preserved LV systolic function. In the subset of patients older than 90 years, about two-thirds had LV ejection fraction (LVEF) greater than 50% (5). In each of these studies, there was a strong female predominance among HFNEF cases. In CHS, women represented 67% of HFNEF cases but only 39% of systolic HF cases (Fig. 2) (4). The typical profile of a HF patient in the community, an elderly woman with preserved LVEF and systolic hypertension, therefore, differs markedly from the typical patient in the HF literature, a middle-aged man with prior myocardial infarction and severely reduced systolic LV function (Table 1) (15). This difference in risk factor profile for systolic HF and HFNEF was further confirmed in a more recent report of over 4500 patients in the population of Olmsted County (16). Patients with HFNEF were older and more likely to be female, have high BMI, hypertension, and atrial fibrillation, and less likely to have coronary artery disease.

The recent update from the Olmsted County project indicates that the incidence of HFNEF is increasing (Fig. 3) (16). In addition, the number of hospitalizations in patients with HFNEF is increasing, in contrast to the hospitalization trend for systolic HF, which is decreasing. Furthermore, Liao et al. (17) recently reported that the total health care cost for HFNEF is at least equal to that of systolic HF. These data, combined with the dearth of information regarding pathogenesis and treatment of this disorder, suggest this syndrome is a health care research priority in older persons.

**Table 1** Heart Failure in Older Versus Middle-Aged Patients

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Elderly</th>
<th>Middle-Aged</th>
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<tbody>
<tr>
<td>Prevalence</td>
<td>6–18%</td>
<td>&lt;1%</td>
</tr>
<tr>
<td>Gender</td>
<td>Predominantly women</td>
<td>Predominantly men</td>
</tr>
<tr>
<td>Etiology</td>
<td>Hypertension</td>
<td>Coronary heart disease</td>
</tr>
<tr>
<td>LV systolic function</td>
<td>Normal</td>
<td>Impaired</td>
</tr>
<tr>
<td>Comorbidities</td>
<td>Multiple</td>
<td>Few</td>
</tr>
</tbody>
</table>

*Abbreviation: LV, left ventricular.*
PROGNOSIS

The morbidity and mortality of older HF patients are perhaps the highest of any chronic CV disorder. In the Olmsted County study, cumulative mortality was 24% at 1 year and 65% at 5 years (5). The mortality increases markedly with age; in a database of 66,547 consecutive first-time admissions for HF in Scotland, one-year case-fatality rate increased from 14% in patients younger than 55 years to 58% in those older than 84 years (18). In community-based individuals aged 65 to 74 years, 10-year mortality was 50% in women and greater than 70% in men (19). Among elderly persons hospitalized for HF, the prognosis is even worse, with five-year mortality greater than 70%; mortality was similar in whites and blacks (20). This age-associated increase in HF mortality observed in numerous studies appears multifactorial. Contributing factors include a generalized reduction in functional reserve, the multiple morbidities seen in elderly patients, and underutilization of medications. Recent data however suggest a modest improvement in survival (7,18). In the Framingham Study, five-year age-adjusted mortality declined from 70% to 59% in men and from 57% to 45% in women between 1950-1969 and the 1990s (7).

Mortality from HFNEF, although substantially higher than in age-matched controls, is about half that reported for systolic HF; in Framingham, the respective annual mortality rates were 8.9% and 19.6% (21). Nearly identical results were seen in CHS (Fig. 4) (22). In elderly patients hospitalized for HF, however, survival appears similar for those with HFNEF versus systolic HF (16,23–26). Given the higher prevalence of HFNEF than systolic HF among the community-based elderly, the population-attributable mortality from HFNEF equals or exceeds that for systolic HF in this age group (22). Predictors of higher mortality in older HF patients resemble those in younger patients and include male sex, LV dilation and systolic dysfunction, diabetes, renal dysfunction hyponatremia, anemia, reduced peak oxygen consumption (VO₂), and recent hospitalization (20,22,27,28). Recent data from Olmstead County suggest that survival in HFNEF did not change over the interval between 1987 and 2001, in contrast to improved survival in patients with systolic HF (16).

Morbidity from HF is also very high in the elderly. Between 30% and 50% of older patients hospitalized for HF will be rehospitalized within three to six months (29–31).

Figure 3  Prevalence of HFNEF in the Olmsted County Population Project (A) is increasing. In the same population, the number of admissions for heart failure is increasing in patients with HFNEF, whereas it is decreasing for systolic HF (B). Abbreviation: HFNEF, heart failure with normal ejection fraction. Source: From Ref. 16.
This high hospitalization rate translates into a poor quality of life and high healthcare costs. Prior admission within one year, prior HF, diabetes, and serum creatinine more than 2.5 mg/dL at discharge predicted readmission in a Medicare database (27). In contrast to mortality, readmission rates appear comparable between HF patients with preserved versus reduced systolic function (26). Other adverse outcomes such as myocardial infarction and stroke are common in older HF patients.

As noted above, older patients frequently have multiple comorbidities, an important distinction from younger HF patients. An important recent analysis of over 122,000 older patients admitted for HF demonstrated that over 95% of patients had at least one noncardiac comorbidity and 55% had four or more noncardiac comorbidities (32). The most common comorbidities were hypertension, diabetes, and chronic obstructive lung disease. As discussed above, another increasingly common comorbidity that may have implications for causality is obesity. In the above study, survival was influenced by the number and type of comorbidities. Indeed, observations suggest that in HFNEF patients the majority of hospital admissions and deaths during follow-up may be due to various cardiac and noncardiac comorbidities, rather than to progressive HF.

**PATHOPHYSIOLOGY**

Given the multiple age-associated changes in CV and non-CV structure and function, and the numerous morbid conditions that often accompany aging, it would not be surprising if the pathophysiology of HF differed in elderly versus younger patients. The limited specific comparative data that exist, particularly the substantially higher prevalence of HF with preserved systolic LV function in older than in younger HF patients, are supportive of differential pathophysiology.

Normal aging is accompanied by a mild concentric thickening of the LV myocardium and reduced early diastolic relaxation and filling rates (33,34). Both of these may derive in part from the age-associated increase in arterial stiffness (35). These findings are similar to those seen in younger hypertensive patients and provide a substrate
more prone to development of diastolic HF. In addition, reduced chronotropic, inotropic, and vasodilator responses to β-adrenergic stimulation occur with advancing age (36–38). The reduced maximal heart rate response to aerobic exercise is a major contributor to the approximately 10% per decade decline in peak oxygen consumption (VO₂) (39,40). Reduced maximal stroke volume, reflecting reduced inotropic and lusitropic reserves, may also contribute to the predilection to HF in some older individuals though not in those screened to exclude occult coronary artery disease (41).

Several non-CV aging changes also contribute to an increased HF susceptibility among the elderly (Table 2). These changes include reduced glomerular filtration rate and ability to excrete a sodium load, increased ventilation perfusion mismatching in the lung, reduced ventilatory capacity, and impaired central nervous system autoregulation.

Many of the morbidities of elderly HF patients are exaggerations of these age-associated physiological changes. Examples include systolic hypertension, LV hypertrophy (LVH), renal dysfunction, and restrictive lung disease. Together, the age-associated changes in CV and non-CV structure and function and the multiple comorbid diseases that occur with advancing age serve to increase susceptibility for developing HF, intensify symptoms and complicate management.

Despite these pathophysiological age differences in the substrate for HF, relatively few studies have specifically compared younger versus older HF patients in this regard. In 128 consecutive patients admitted with HF, Cody et al. (42) observed a reduced heart rate and increased systemic vascular resistance at rest in older patients and a reduced heart rate response to tilt. Plasma norepinephrine increased with age, whereas no consistent age trends were seen for plasma renin activity or urinary aldosterone. A reduction of glomerular filtration rate and filtration fraction and increases in renal vascular resistance and serum creatinine levels were observed at older ages (42). In a comparison of HF outpatients older than 75 years to those younger than 65 years, Dutka et al. (43) observed that the older group had substantially smaller ventricles, higher fractional shortening, higher Doppler A-wave velocity, lower E/A ratio, and longer deceleration time than the younger group. The findings of better systolic function and impaired diastolic performance in the older group are noteworthy because all patients in this study were required to have fractional shortening of less than 28%, indicating LV systolic

<table>
<thead>
<tr>
<th>Condition</th>
<th>Implications</th>
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<tbody>
<tr>
<td>Renal dysfunction</td>
<td>Worsens symptoms, prognosis; exacerbated by diuretics, ACE inhibitors</td>
</tr>
<tr>
<td>Chronic lung disease</td>
<td>Worsens symptoms, prognosis; contributes to uncertainty about diagnosis/volume status</td>
</tr>
<tr>
<td>Cognitive dysfunction</td>
<td>Interferes with dietary, medication, activity compliance</td>
</tr>
<tr>
<td>Depression, social isolation</td>
<td>Worsens prognosis, interferes with compliance</td>
</tr>
<tr>
<td>Postural hypotension, falls</td>
<td>Exacerbated by vasodilators, diuretics, β blockers</td>
</tr>
<tr>
<td>Urinary incontinence</td>
<td>Aggravated by diuretics, ACE inhibitors (cough)</td>
</tr>
<tr>
<td>Sensory deprivation</td>
<td>Interferes with compliance</td>
</tr>
<tr>
<td>Nutritional disorders</td>
<td>Exacerbated by dietary restrictions</td>
</tr>
<tr>
<td>Polypharmacy</td>
<td>Compliance issues, drug interactions</td>
</tr>
<tr>
<td>Frailty</td>
<td>Worsens symptoms and quality of life; exacerbated by hospitalization; increased fall risk</td>
</tr>
</tbody>
</table>

Abbreviation: ACE, angiotensin-converting enzyme.
dysfunction. These investigators confirmed higher levels of plasma norepinephrine in older patients but observed lower plasma renin, angiotensin, and atrial natriuretic peptide than in younger patients (43). Of note, 30% of the older group but none of the younger group had atrial fibrillation, similar to the observation of Wong, et al. (44). Although Clark and Coats observed no age-associated decline in peak VO2 in 68 HF patients with mean LVEF of 22% (45), others have reported greater reduction of aerobic capacity in elderly HF patients than in middle-aged HF patients (46).

As previously discussed, a majority of older HF patients have preserved systolic function (4,5,14,15,21). This syndrome is relatively uncommon in younger HF patients, and represents the starkest difference in HF as it commonly presents in older than in younger populations. Compared with systolic HF, there is a relative paucity of information regarding the pathophysiology of HFNEF. Exercise intolerance, manifested as exertional dyspnea and fatigue, is the primary symptom in chronic HF, with either a reduced or a normal ejection fraction. Three separate studies have now demonstrated that HFNEF patients have severely reduced exercise capacity as measured objectively by peak VO2 during exercise and that their exercise intolerance is just as severe as that of age-matched systolic HF patients (Fig. 5) (46–48).

Understanding the mechanisms of the reduced oxygen consumption in elderly HFNEF patients could provide important insight into the pathogenesis of this important disorder as well as potential therapy. Using invasive cardiopulmonary exercise testing, it was demonstrated that HFNEF patients have a reduced ability to increase stroke volume via the Frank-Starling mechanism despite severely increased LV filling pressure, indicative of diastolic dysfunction (Fig. 6) (47). This process resulted in severely reduced exercise cardiac output and early lactate formation and was a significant independent contributor to the severely reduced exercise capacity and associated chronic exertional symptoms (47).

Another study indicated that decreased aortic distensibility, likely due to the combined effects of aging- and hypertension-induced thickening and remodeling of the thoracic aortic wall, is an important contributor to exercise intolerance in chronic HFNEF (48). Compared with age-matched healthy subjects, patients with HFNEF had increased pulse pressure and thoracic aortic wall thickness and markedly decreased aortic distensibility that correlated closely with their severely decreased peak VO2 ($r = 0.8$; $p < 0.001$) (Fig. 7) (48). Similar data have been reported for patients with systolic HF (49).
Figure 6  Left ventricular diastolic function assessed by invasive cardiopulmonary exercise testing in patients with heart failure and normal systolic function (open boxes) and age-matched normals (closed boxes). Pressure-volume relation was shifted upward and leftward at rest. During exercise, left ventricular diastolic volume did not increase in the patients, despite marked increase in diastolic (pulmonary wedge) pressure. Due to diastolic dysfunction, failure of the Frank–Starling mechanism resulted in severe exercise intolerance. Source: From Ref. 47.

Figure 7  Data and images from representative subjects from healthy young, healthy elderly, and elderly patients with heart failure. Maximal exercise oxygen consumption (Vo2 max), aortic distensibility at rest, and left ventricular mass:volume ratio. Patients with diastolic heart failure have severely reduced exercise tolerance (Vo2 max) and aortic distensibility and increased aortic wall thickness. Source: From Ref. 48.
With advancing age, there is a modest decline in flow-mediated arterial dilation (FMAD) in large arm and leg arteries. In systolic HF, it had previously been shown that brachial FMAD is severely reduced and may contribute to exercise intolerance in these patients. It has been assumed that HFNEF patients may have similar abnormalities in FMAD as those with systolic HF. However, Hundley et al. (50), using magnetic resonance measures of flow and cuff occlusion in three well-defined groups of subjects (systolic HF, HFNEF, and age-matched healthy volunteers), showed that while FMAD in the femoral artery is substantially reduced in older patients with systolic HF compared with normal age-matched subjects, in patients with HFNEF it is relatively preserved. These investigators also performed peak exercise testing in these subjects. The data confirmed the previous report of a similar degree of exercise intolerance in HFNEF and systolic HF, in stark contrast to the FMAD results, thus indicating that significant abnormalities in FMAD are unlikely to contribute significantly to exercise intolerance in these patients.

It has long been recognized, though underappreciated, that patients with systolic HF as a group have chronotropic incompetence, and that this contributes to their exercise intolerance. Brubaker et al. (51), were the first to report that chronotropic incompetence is also a significant contributor to exercise intolerance in older patients with HFNEF. As in the study by Hundley et al. above (50), the study design included a positive control group (age-matched patients with systolic HF), a HFNEF group, and a neutral control (age-matched healthy volunteers screened for occult CV disease) group. All the three groups underwent upright bicycle exercise to exhaustion with detailed physiological measurements, included expired gas analysis. The prevalence of chronotropic incompetence, defined by published criteria, was 22% in systolic HF patients, 20% in HFNEF, and 7% in healthy volunteers. Among HF patients, those with chronotropic incompetence had considerably greater exercise intolerance, assessed as peak oxygen consumption, and in multivariate analyses, chronotropic incompetence was an independent contributor to exercise intolerance (51). The contribution of chronotropic incompetence to exercise intolerance in HFNEF was confirmed by Borlaug et al. (52).

It is very likely that systolic hypertension plays an important role in the genesis of HFNEF in the elderly. In animal models, diastolic dysfunction develops early in systemic hypertension, and LV diastolic relaxation is very sensitive to increased afterload (53–55). Increased afterload impairs LV relaxation, leading to increased LV filling pressures, decreased stroke volume, and symptoms of dyspnea and congestion (55). Nearly all (88%) HFNEF patients have a history of chronic systemic hypertension (4,56). In addition, severe systolic hypertension is usually present during acute exacerbations (pulmonary edema) (57,58).

Although the role of ischemia in HFNEF is uncertain, it would seem likely that it is a significant contributor in many cases. It had been hypothesized that patients found to have a normal ejection fraction following an episode of HF may have had transiently reduced systolic function and/or ischemia at the time of the acute exacerbation. If so, then the term “HFNEF” would be an inappropriate label for this disorder and all therapeutic efforts would be aimed at therapy of ischemia and reversible systolic dysfunction. One study addressed this important issue by performing echocardiograms at the time of presentation in 38 consecutive patients with acute hypertensive pulmonary edema and again about three days later after resolution of pulmonary edema and hypertension (58). The LVEF and wall motion score index at follow-up were similar to those found during the acute echocardiogram. Of those who had LVEF ≥50% at follow-up (n = 18), all but two had LVEF ≥50% acutely, and in those two cases, the LVEF was more than 40%, above the level which would be expected to cause acute HF on the basis of primary
systolic dysfunction (Fig. 8). These data suggest that marked transient systolic dysfunction does not often play a primary role in patients presenting with acute HF in the presence of severe systolic hypertension who are subsequently found to have a normal ejection fraction. Furthermore, these findings indicate that the ejection fraction measured at follow-up accurately reflects that measured during an acute episode of HF. This study and a related study, in which pulmonary edema recurred in about half of such patients despite coronary revascularization, support the concept that acute pulmonary edema in these patients is most likely due to an exacerbation of diastolic dysfunction caused by severe systolic hypertension rather than by ischemia (57).

Neurohormonal activation is felt to play an important, even fundamental, role in the pathophysiology of systolic HF. In a group of patients with HFNEF, Clarkson et al. (59) showed that plasma atrial natriuretic peptide and brain natriuretic peptide were substantially increased and there was an exaggerated response during exercise, a pattern similar to that described in patients with systolic HF. Furthermore, atrial natriuretic peptide levels among older frail subjects are predictive of the subsequent development of HF (60). In a study using two different control groups, age-matched healthy normal subjects and age-matched systolic HF patients, Kitzman et al. (46) showed that older patients with HFNEF have markedly increased plasma norepinephrine levels, equivalent to those seen in systolic HF and had levels of atrial and brain natriuretic peptide that were 10-fold increased compared with age-matched normals. In the above study, HFNEF patients were also shown to have severely reduced health-related quality of life, a potentially important therapeutic target.

Although HFNEF has been presumptively termed “diastolic heart failure,” the precise role of diastolic dysfunction in this disorder has been somewhat controversial (61–64). In a prior study that did not include more recently developed tissue Doppler techniques, noninvasive blood flow Doppler measures of LV diastolic filling were similar between patients with systolic HF and those with HFNEF (46). In studies where LV...
pressures and volume were studied invasively, the LV pressure volume relationship was shifted upward and to the left in most patients, indicative of diastolic dysfunction (47,65,66).

Given the high prevalence of hypertension, it has also been thought that patients with HFNEF would usually have evidence of significant LVH. Indeed, in an earlier study with young and old healthy normal control groups, there was evidence of increased LV mass/volume ratio, reflecting their concentric hypertrophic remodeling (46). A recent analysis from the CHS by Maurer et al. (67) indicates that LVH may not necessarily be more common in older patients with HFNEF than in age-matched patients with hypertension but not HF. Further, overall diastolic LV size tended to be modestly increased in those with HFNEF, rather than decreased, as one would expect with concentric remodeling 67).

Likely contributing to the variability in reports is the major influence of sex and body size on measures of LV mass and chamber size, and the difficulty in adjusting for their impact. Another potential contributor may be differences in case definition. It seems likely that changes in diastolic function and myocardial mass and composition contribute prominently to HFNEF. However, given the marked heterogeneity in LV function and morphometry seen in the more familiar and well-studied syndrome of systolic HF, the possibility of substantial heterogeneity in HFNEF should not be unexpected.

Recent reports also indicate that renal dysfunction (30) and anemia (68) contribute to pathogenesis and symptoms in a significant number of patients with HFNEF. This possibility too should not be surprising given similar data in patients with systolic HF, all the more because of the older average age of HFNEF patients. In a follow-up study of patients initially hospitalized with HFNEF, Brucks et al. (68) showed that the degree of anemia was an independent predictor of mortality.

The role of genetic predisposition in the genesis of HFNEF in the elderly is not known. However, data from the Hypertension Genetic Epidemiology Network (HyperGEN) study have shown significant heritability of hypertension, (69) LV mass, (70) and Doppler diastolic filling, (70) all factors that likely play a role in HFNEF in the elderly. In addition, genetic factors have now been identified in patients with hypertrophic cardiomyopathy, a disorder that shares a number of features with HFNEF in the elderly. In addition, mutations that result in aldosterone excess or abnormal aldosterone handling result in morphology and symptoms suggestive of early HFNEF. The preponderance of female sex in HFNEF may also help understand its pathogenesis. Among healthy normal subjects, older women tend to have higher LV ejection fractions, independent of their smaller chamber size, than in men (71). Also, the female left ventricle in mammals has a distinctly different response to pressure load, such as is typical of systemic hypertension. In the HyperGEN study, it was found that the deceleration time of early diastolic flow and isovolumic relaxation time were lengthened in hypertensive women compared to men, independent of all other factors, indicative of decreased myocardial relaxation (72). Among hypertensives in the Framingham Study, the predominant pattern of hypertrophic remodeling in women was concentric, whereas in men it was eccentric; this pattern has also been reported in several other studies, including HyperGEN (72) and Losartan Intervention for Endpoint Reduction (LIFE) (73).

Using aortic banding to create a model of chronic LV pressure overload in male and female rats, Douglas et al. (74) showed that male rats responded with LV dilation and modest wall thickening (eccentric hypertrophy) with resultant increased wall stress and decreased LV contractility. In contrast, the female rats increased their LV wall thickness and maintained a normal chamber size (concentric hypertrophy), and thereby enjoyed near-normal wall stress, and normal (even a trend toward supranormal) contractility. As a
result, the female rats were able to continue to generate substantially higher systolic pressure, despite the excess afterload. Other studies have shown similar overall results (75,76).

Large population-based studies have consistently shown that the strongest, most common risk factor for the development of HF is systolic hypertension. Combining this key point with the findings of the Douglas et al. (75) study provides a cohesive explanation for the divergent manifestations of HF in women versus men. The male left ventricle is less able to tolerate pressure load, and in the presence of chronic systolic hypertension becomes dilated with thin walls and a depressed ejection fraction. The female left ventricle is able to tolerate the pressure load better by developing concentric hypertrophy, allowing it to maintain normal LV size and ejection fraction. However, the cost of this adaptation is impaired LV diastolic function. This finding may help to explain why men tend to develop systolic HF, whereas women tend to develop HFNEF. The above interplay between LV remodeling and pressure load has been shown in rodent models to be influenced substantially by estrogen and androgen, and to be related to gender differences in cardiac angiotensin-converting enzyme (ACE) expression (77).

PRECIPITANTS

Relatively few published data exist regarding the specific precipitants of HF in the elderly. In a series of 154 consecutive HF patients aged 75 ± 8 years admitted to an Italian geriatrics ward, 71% had coronary artery disease, 45% hypertension, and 32% valvular heart disease (78). Factors precipitating HF were evident in 62% of patients and included atrial fibrillation (16%), lack of drug compliance (10%), renal failure (8%), fever (7%), and anemia (6%). The important contribution of atrial fibrillation to the development of HF in the elderly has been observed in multiple studies and probably relates to the greater reliance of older versus younger patients on the atrial contribution to LV filling. In this elderly group, 45% of whom had normal LV systolic function, the presence of HF was associated with an average of five unrelated diseases (78). In the Established Population for Epidemiological Studies of the Elderly (EPESE) community-based cohort, myocardial infarction was the precipitant of HF in 49 of 173 cases (28%) (9).

Acute elevations of blood pressure appear responsible for a significant proportion of patients presenting with acute pulmonary edema (57,58). It is difficult in such patients, however, to determine whether the elevated blood pressure seen at presentation was the primary precipitant of HF or was secondary, at least in part, to the heightened sympathetic tone associated with acute pulmonary edema. That hypertension per se rather than ischemia is responsible for many such episodes is suggested by the finding that of 19 patients who underwent coronary revascularization after presenting with acute pulmonary edema, nine were rehospitalized with pulmonary edema over the next six months (57).

Hypothyroidism and hyperthyroidism should always be considered in older patients presenting with new-onset HF. Some antihyperglycemics have in some studies been reported to be associated with new-onset HF. However, most of these analyses are confounded by cause and effect, the high prevalence and incidence of HF among diabetics, and retrospective and ad hoc analysis designs. Another frequent confounder is pneumonia, which frequently masquerades as HF or precipitates HF in older patients admitted with acute dyspnea.
DIAGNOSIS AND CLINICAL FINDINGS

Given that HF is a clinical syndrome rather than a specific disease, the diagnosis is based on a constellation of findings rather than on a specific clinical feature or laboratory test. Unfortunately, this observation has led to a variety of diagnostic criteria for HF, none of which is universally accepted. Further complicating matters is the recent introduction of proposed definitions for diastolic versus systolic HF (79,80).

Making a diagnosis of HF in the elderly is particularly challenging for several reasons. First, many of the symptoms and signs of HF are similar to those of other disorders that are frequent among the elderly (Table 3). Next, many elderly patients may be unable to give an adequate history because of cognition or sensory impairments. In addition, many older patients will consciously or unconsciously reduce their level of physical activity, thereby masking the two cardinal symptoms of exertional dyspnea and fatigue. It is therefore useful to ask patients to detail recent changes in their activity levels and exercise tolerance. Furthermore, elderly patients, including those with HF, often present with atypical, nonspecific symptoms, such as weakness, fatigue, somnolence, confusion, and disorientation. Finally, the frequent occurrence of a normal LVEF in older HF patients may lead the clinician away from the correct diagnosis.

Although the Framingham criteria for HF (81) have been frequently cited, they have not been validated in a purely elderly population, and their applicability to clinical practice and research trials have not been rigorously tested. Rich et al. (29) proposed simplified, practical criteria for the diagnosis of HF in elderly patients. These are a history of acute pulmonary edema, or the occurrence of at least two of the following with no other identifiable cause and with improvement following diuresis: dyspnea on exertion, paroxysmal nocturnal dyspnea, orthopnea, bilateral lower extremity edema, or exertional fatigue. In a series of 154 consecutive Italian geriatric patients hospitalized with HF, the most common signs and symptoms were pulmonary rales (77%), orthopnea (73%), edema

Table 3  Alternate Explanations for Signs/Symptoms Suggestive of CHF in Elderly Patients

<table>
<thead>
<tr>
<th>Signs/Symptoms Suggestive of CHF in Elderly Patients</th>
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<tbody>
<tr>
<td>Dyspnea and rales</td>
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<tr>
<td>- chronic pulmonary disease</td>
</tr>
<tr>
<td>- pneumonia</td>
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<tr>
<td>Pedal edema</td>
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<tr>
<td>- benign idiopathic edema</td>
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<tr>
<td>- primary venous insufficiency</td>
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<tr>
<td>- renal or hepatic disease</td>
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<tr>
<td>- medications</td>
</tr>
<tr>
<td>Fatigue</td>
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<tr>
<td>- anemia</td>
</tr>
<tr>
<td>- hypothyroidism</td>
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<tr>
<td>- extreme obesity</td>
</tr>
<tr>
<td>- severe deconditioning</td>
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<tr>
<td>Aortic or mitral stenosis/regurgitation</td>
</tr>
<tr>
<td>Constrictive pericarditis</td>
</tr>
<tr>
<td>Ischemic heart disease</td>
</tr>
<tr>
<td>Cautions</td>
</tr>
<tr>
<td>- Elderly often have multiple confounding conditions</td>
</tr>
<tr>
<td>- Normal aging alone does not cause exertional fatigue, dyspnea</td>
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</tbody>
</table>

Abbreviation: CHF, chronic heart failure.
(62%), paroxysmal nocturnal dyspnea (56%), gallop rhythm (45%), and jugular venous distension (32%) (78).

Despite statistical associations between various demographic/clinical findings and normal versus reduced LV systolic function in HF populations, none is reliable enough to obviate the need for measuring LV performance. Thus, evaluation of new HF in any patient, young or old, should include an imaging test. An echocardiogram is usually the preferred initial imaging procedure because it can detect important structural disorders such as aortic or mitral valvular disease, hypertrophic cardiomyopathy, cardiac amyloidosis, or pericardial effusion, in addition to assessing LV systolic and diastolic performance.

Whereas general agreement exists that a LVEF lower than 40% to 45% represents reduced systolic function, the substrate for systolic HF, a definitive noninvasive measure for diastolic dysfunction is not available. Doppler LV diastolic filling indices vary with LV load and with normal aging. The patterns of filling are helpful, and the newer tissue Doppler techniques are particularly promising (82). Nevertheless, their role in the diagnosis and management of HFNEF remains unclear. Some have believed that invasive measurements are needed to definitively confirm the presence of diastolic dysfunction. However, an important study demonstrated that measurement of diastolic function, either invasive or noninvasive, may be unnecessary in most patients (83). This study found that in patients with LVH and symptoms compatible with HF, nearly all had abnormal diastolic function when measured invasively.

The diagnosis of HFNEF should probably be viewed as one of exclusion (46). However, most persons who have typical HF symptoms and typical demographics of HFNEF (older women with history of hypertension) will not be found to have other explanations for their symptoms and probably have this disorder. Among other explanations for symptoms, obesity deserves special mention. Although severe obesity, per se, can cause exertional symptoms, large epidemiological studies show that classic systolic HF is associated with significantly increased body weight and body mass index, even when patients are at “dry weight.” Further, in longitudinal studies, obesity is a common precursor to HF. As a group, elderly HFNEF patients have increased body weight similar to that of patients with confirmed systolic HF (6,22). Thus, in a patient with otherwise typical features, mild-to-moderate obesity alone should not exclude the diagnosis of HFNEF. As discussed earlier in this chapter, obesity is both a major independent risk factor for developing HF as well as a potential confounder in its diagnosis.

TREATMENT

General Considerations

The treatment goals in older HF patients, whether accompanied by normal or reduced systolic function, resemble those for any chronic disorder and include relief of symptoms, improvement in functional capacity and quality of life, prevention of acute exacerbations, and prolongation of survival. In the elderly, however, the latter goal is generally less important than preservation of independence and a satisfactory quality of life. A systematic management plan should incorporate attention to diet, physical activity and other lifestyle factors, avoidance of aggravating conditions, careful titration of medications, and frequent follow-up. Adequate education of patient and/or caregiver and enhancement of their disease management skills can also reap major benefits. The management team might involve a nurse, dietician, pharmacist, social worker, and physical therapist, in addition to the attending physician.
Over the past decade, the value of multidisciplinary HF management programs has been repeatedly demonstrated to reduce HF exacerbations and re-hospitalizations, reduce costs, and improve quality of life (29, 84–86). One study also suggested enhanced survival (Fig. 9) (84). HF management programs can also rectify the substantial underutilization of proven therapies like ACE inhibitors and β-adrenergic blockers known to occur in elderly HF patients (87). Such programs emphasize frequent contact with health care providers to avoid acute decompensation, and typically utilize periodic phone calls, frequent follow-up visits and monitoring programs, including via the Internet. Adjustment of diuretics can be made by nurses over the telephone or by the patients themselves, using simple algorithms. Adjunctive strategies such as elimination of tobacco and alcohol, appropriate administration of influenza and pneumococcal vaccines, minimized use of sodium-retaining medications, and use of cardiac rehabilitation should also be addressed. Common HF precipitants such as atrial fibrillation, anemia, renal failure, and pulmonary infections should be aggressively treated.

Recent reports have detailed a high prevalence of anemia in HF populations and its adverse effects in this setting, including reduced exercise tolerance, higher rehospitalization rates, and increased mortality. Although a few small studies have suggested that treatment of low hemoglobin levels using erythropoiesis-stimulating proteins may improve cardiorenal function and exercise tolerance in patients with severe HF, a recent, randomized trial in older patients (mean age 71 years) showed no significant increase in aerobic capacity after six months of darbopoeitin treatment, though health-related quality of life improved (88).

**Diet**

Despite wide recognition that indiscreet use of sodium is a common cause of HF exacerbations, few objective data exist regarding the optimal sodium intake for a HF patient of any age. Moderate sodium restriction to about 2 g/day is adequate to prevent weight gain in most stable patients. More severe sodium restriction may allow a reduction in diuretic dose but is often impractical for patients to maintain. Water restriction is not usually necessary unless significant hyponatremia is present. The age-associated reduction in glomerular filtration rate seen in HF patients adds to the complexity of maintaining proper sodium balance in the elderly.
PHYSICAL ACTIVITY

Given that exercise intolerance is a hallmark of the HF syndrome, it seems logical that HF patients would derive a significant benefit from exercise training. Surprisingly, the potential benefits of aerobic training programs in such patients were not widely recognized until the past decade. Although several prospective trials have now demonstrated substantial increases in peak VO₂, cardiac output, and other physiological parameters in patients with systolic HF, these studies included very few patients older than 70 years, very few women, and no diastolic HF patients (89). Nevertheless, those few trials that have enrolled meaningful numbers of older patients have shown similarly favorable results. In the largest trial to date, Austin et al. (90) randomized 200 patients aged 60–89 years (mean age 72 years) with systolic HF to a 24-week program of combined aerobic and low resistance strength training versus usual care. Significant improvements were found in health-related quality of life, New York Heart Association (NYHA) class, and six-minute walk distance among exercisers, whereas no changes occurred in controls (90). A recent observational study suggested that exercise training may also improve exercise capacity and quality of life in patients with HFNEF; these benefits were unrelated to changes in Doppler indices of diastolic filling (91).

Probably, the most important limitation of existing HF training studies is that none has been adequately powered to definitively address the impact on survival. A modest-sized trial by Belardinelli et al. (92) observed a 71% reduction in HF hospitalizations and 63% lower mortality among 50 patients assigned to exercise training compared with 49 controls over 14 months of follow-up. An ongoing National Heart, Lung, and Blood Institute–sponsored, multicenter, randomized trial involving two years of aerobic exercise training in over 2300 systolic HF patients with LVEF of less than or equal to 35% should provide a definitive answer regarding the impact of this intervention on mortality and morbidity in both younger and older HF patients (93).

PHARMACOTHERAPY FOR SYSTOLIC HF

During the past two decades, numerous randomized trials have defined the role of ACE inhibitors, angiotensin-receptor blockers (ARB), other vasodilators, β-adrenergic blockers, digitalis and other inotropes, and various other drugs in patients with HF and reduced systolic function. Although many of the studies from the 1980s and early 1990s included very few elderly patients and women, more recent trials have generally been less restrictive. Thus, the strength of the data defining the relative benefits of these drugs in the elderly varies widely among studies.

Diuretics

Diuretics provide the cornerstone for prompt symptomatic relief and control of pulmonary congestion and peripheral edema in HF patients. Perhaps for this reason, they have been the subjects of very few randomized HF clinical trials. Although they are needed to control fluid retention in most patients, no diuretic other than spironolactone has been shown to reduce HF mortality. Furthermore, their potential for reducing renal function, causing multiple electrolyte derangements, and exacerbating the hyperactivity of the renin-angiotensin system dictate that they be titrated to the lowest effective dose, especially in the elderly. Most HF patients will require a loop diuretic to maintain euvoolemia, though a thiazide may suffice in some patients with mild HF and a glomerular
filtration rate of greater than 30 mL/min. Patients with more severe fluid retention or concomitant renal dysfunction may require the addition of metolazone 2.5 to 10 mg/day.

Because most patients have an intrinsic diuretic threshold below which diuresis will not occur, a single morning dose above this threshold is more effective than multiple subthreshold doses. In patients with nocturnal congestive symptoms, a twice-daily regimen may be necessary. Systemic steroids or nonsteroidal anti-inflammatory drugs, commonly used in the elderly, should be discontinued or used at the lowest possible dose because of their sodium-retaining properties. Careful monitoring of fluid and electrolyte balance is necessary during active diuresis, with replacement of potassium, magnesium, and chloride as necessary. Fluid restriction may be needed if hyponatremia occurs. Need for escalating doses of diuretics in a previously stable patient suggests medication and/or dietary noncompliance, poor drug absorption due to bowel edema, a concomitant exacerbating condition or medication, or progression of the underlying cardiac disorder.

ACE Inhibitors

Numerous studies across varying patient profiles have established ACE inhibitors as a critical component of drug therapy for systolic HF. In the landmark Cooperative North Scandinavian Enalapril Survival Study (CONSENSUS) trial, the first study to demonstrate their beneficial effect on mortality, enalapril 10 to 20 mg twice daily reduced six-month mortality from 48% to 29% in older patients with NYHA class IV systolic HF despite diuretics and digitalis; the mortality benefit and symptomatic improvement were similar in patients older and younger than the median age of 70 years (94). Subsequent studies have confirmed that these salutary effects of ACE inhibitors on survival and quality of life are not diminished in the elderly (95). These findings indicate that ACE inhibitors should be initiated in essentially all elderly systolic HF patients without contraindications to their use. The primary relative contraindication is advanced renal dysfunction.

ACE inhibitors are thought to be beneficial in HF compared to other vasodilators because they antagonize the renin-angiotension system, whose activation is thought to be pivotal to disease progression and adverse prognosis in HF patients. Although they have minimal effect on cardiac function, they inhibit the progressive LV dilation that occurs in patients with systolic HF (96,97). This effect is particularly prominent in patients with reduced systolic function after myocardial infarction (96).

As with other drugs in the elderly, ACE inhibitors should be initiated at low doses and increased slowly toward the doses proven effective in clinical trials with careful monitoring for adverse effects. The most common effects limiting full dosing are hypotension and worsening renal function. To minimize the risk for hypotension, volume depletion should be corrected before the first dose is administered, especially in patients with systolic blood pressure (SBP) of less than 100 mmHg, severe LV dysfunction, or hyponatremia. A mild dry cough develops in up to 5% of patients but is not age related and often regresses over time. Even when persistent, it can often be tolerated when patients understand the significant survival advantage imparted by the ACE inhibitor drug (98). Among patients who are unable to tolerate standard doses of ACE inhibitors, data from the Assessment of Treatment with Lisinopril and Survival (ATLAS) study suggest that doses of the long-acting ACE inhibitor lisinopril as low as 2.5 to 5 mg daily may be beneficial (99). Interestingly, this effect was observed particularly in older individuals.

Of the many ACE inhibitors currently available, all except captopril allow once or twice daily dosing to optimize compliance. Despite claims of between-drug differences in tissue penetration or other properties of ACE inhibitors, the clinical literature suggests
similar benefits among ACE inhibitors used in systolic HF. Three ACE inhibitors are now available in generic formulations, and two of them, enalapril and lisinopril, are long acting. Health care providers should familiarize themselves with the local costs of the available ACE inhibitors to minimize the financial burden on their older patients.

**Angiotensin-Receptor Blockers**

Similar to ACE-inhibitors, agents in this newer drug class also antagonize the renin-angiotensin system. ARBs have not been definitively proven to be equivalent to ACE inhibitors in reducing morbidity and mortality in HF patients of any age. Although the Losartan Heart Failure Survival Study [Evaluation of Losartan In The Elderly (ELITE-1)] suggested a survival advantage of the ARB losartan over the ACE inhibitor captopril in patients aged 65 years and older (100), the larger ELITE-2 study failed to confirm this finding; annual mortality was 11.7% with losartan and 10.4% with captopril, a statistically nonsignificant difference (101). Given the more voluminous literature establishing the benefits of ACE inhibitors, and the statistically nonsignificant trend favoring them compared to ARBs seen in ELITE-II, ACE inhibitors remain the preferred initial agents. An advantage of ARBs over ACE inhibitors is a lower incidence of cough. Although ELITE-I demonstrated that contrary to the primary study hypothesis the overall incidence of renal dysfunction and other side effects is not lower with ARBs than with ACE inhibitors (101), in both studies, discontinuation of study drug was less common with losartan. Thus, for patients unable to tolerate an ACE inhibitor, an ARB is a suitable alternative. In most settings, generic ACE inhibitors are available at considerably lower cost to the patient than ARBs.

The addition of an ARB to patients who remain symptomatic despite maximal doses of ACE inhibitors may improve symptoms and exercise tolerance. This combination was associated with more favorable LV remodeling than either agent alone in the Randomized Evaluation of Strategies for Left Ventricular Dysfunction (RESOLVD) trial (102). However, in the Valsartan Heart Failure Trial (VALHEFT), the combination of an ACE inhibitor and ARB did not reduce the primary endpoint of all cause mortality but effected a 28% reduction in hospitalization and improved quality of life (103). This effect, however, was not seen in persons who were also taking β blockers. The cost of combination ARB/ACE inhibitor therapy, which is much higher than generic ACE inhibitor alone, should be taken into consideration. In VALHEFT, the small subgroup not on ACE inhibitors at baseline (mean age 67 years) experienced a 45% reduction in all-cause mortality, confirming ARBs as an acceptable alternative in patients proven intolerant of ACE inhibitors (103). Similarly, in the Candesartan in Heart Failure Assessment of Reduction in Morbidity and Mortality (CHARM)–Alternative Study, candesartan 32 mg daily reduced the incidence of CV death or HF hospitalization by 30% versus placebo in patients with systolic HF who were intolerant of ACE inhibitors (104). In the CHARM-Added trial, addition of candesartan 32 mg daily to a regimen including ACE inhibitors reduced this combined endpoint by 15% (104).

**Aldosterone Antagonists**

The aldosterone antagonist and mild diuretic spironolactone 25 mg daily was recently shown to reduce mortality by 27% in patients with NYHA Class III or IV HF in the Randomized Aldactone Evaluation Study (RALES) (105). The mortality benefit was similar in younger and older patients and was thought to be independent of its weak
diuretic effect (106). Painful gynecomastia occurs in up to 10% of patients during chronic therapy, but is lower in women. Eplerenone, a highly selective aldosterone antagonist, has fewer endocrine side effects than spironolactone, including a lower incidence of gynecomastia. In the Eplerenone Post-Myocardial Infarction Heart Failure Efficacy and Survival Study (EPHESUS), 50 mg of eplerenone added to standard medical therapy reduced morbidity and mortality within 30 days in patients with systolic HF complicating acute myocardial infarction (108). Of note, this benefit was statistically significant in patients younger than 65 years, but not in older patients. Current guidelines recommend using aldosterone antagonists in systolic HF patients with moderately severe-to-severe symptoms despite treatment with a diuretic, an ACE inhibitor, and a β-blocker, if there is preserved renal function and normal serum potassium (107).

Hydralazine and Isosorbide Dinitrate

The vasodilator combination of hydralazine 75 mg q.i.d. and isosorbide dinitrate 40 mg q.i.d. used in Veterans Administration Cooperative Vasodilator-Heart Failure Trial I (VHEFT I) was the first drug regimen shown to prolong life in HF patients (109). However, VHEFT II established that ACE inhibition with enalapril was superior to this combination in reducing mortality (110). Further disadvantages of this combination are its q.i.d. dosing requirement, low tolerability, and minimal experience in women and elderly patients. Hydralazine and isosorbide dinitrate may nevertheless represent an alternative for patients with contraindications or intolerance to ACE inhibitors or ARBs. Renewed interest in this drug combination was generated by the African-American Heart Failure Trial (A-HeFT), which found that combined hydralazine-isosorbide dinitrate added to standard “triple therapy,” with diuretics, ACE inhibitors, and β-blockers, reduced mortality by 43% and first HF hospitalization by 33% in African-American patients with systolic HF (111). However, the mean age of 57 years and predominance of nonischemic HF etiology in the study population raise questions about its applicability to elderly African-Americans with HF.

Other Vasodilators

Early trials with intravenous nesiritide (human B-type natriuretic peptide) improved symptoms in patients with acutely decompensated HF and appeared safer than dobutamine (112,113). Recent pooled analyses, however, suggest increased risk of worsening renal function (114) and higher risk of death (115) with this drug. The oral vasopressin antagonist tolvaptan reduced signs and symptoms of congestion in patients hospitalized for acute HF and systolic dysfunction (116,117) but did not affect mortality or HF-related morbidity over a median 10-month follow-up period (117). The mean age of patients in these trials was in the low-to-mid 60s; analyses specific to the elderly have not been presented.

β-Adrenergic Blockers

Multiple large randomized trials that included up to 80 years old have shown that β-adrenergic blockers reduce all-cause mortality and hospitalizations and improve symptoms in systolic HF; benefits are similar in older versus younger patients (118–120). Nevertheless, relative contraindications to β-blockade such as conduction system disturbances, obstructive lung disease, and claudication are more prevalent among the
elderly and may limit the achievement of maximal recommended doses. In all age groups, β blockers should be started at very low doses (carvedilol 3.125 mg twice daily, extended-release metoprolol 12.5 mg daily) in clinically stable patients receiving appropriate doses of ACE inhibitors and diuretics; upward dose titrations should occur at intervals of two weeks and more.

The Carvedilol or Metoprolol European Trial (COMET) demonstrated that carvedilol titrated to a target dose of 25 mg bid reduced all-cause mortality by 17% compared with metoprolol tartrate (target dose 50 mg bid) (121). In this trial, a similar benefit of carvedilol on mortality was seen in patients older than 65 years versus younger patients (121). Whether a similar benefit of carvedilol is present compared with the newer, more commonly used sustained-release metoprolol succinate is unclear. Of particular relevance to the elderly, a European trial with β₁-selective blocker nebivolol reduced the risk of death or CV hospitalization by 14% in patients older than 70 years (mean age 76) and LVEF of less than 35% or hospital admission for HF within the previous year (122). In a recent subanalysis from this trial, the benefit varied directly with the nebivolol dose achieved, even after adjustment for known risk factors.

Digoxin

Despite its use in HF for more than 200 years, the definitive role of digitalis in this setting has been clarified only within the past decade. The multicenter Digitalis Investigation Group (DIG) study randomized nearly 6800 HF patients in sinus rhythm with LVEF of less than and equal to 45% on ACE inhibitors and diuretics to digoxin or placebo (123). Over 37 months of mean follow-up, digoxin had no effect on mortality but reduced HF symptoms and hospitalizations by 28%. The effects of digoxin were similar across age groups, including those 80 years and older (124). The drug is therefore recommended in HF patients who remain symptomatic on diuretics and ACE inhibitors. Digoxin may be particularly useful in those HF patients with atrial fibrillation in whom it can help control ventricular rate. The age-associated reduction in its volume of distribution and in its renal clearance, however, result in higher serum digoxin levels in older versus younger patients given a fixed digoxin dose (125). Furthermore, serum digoxin levels greater than 1.5 ng/dL are accompanied by increased toxicity but no greater efficacy than lower doses among the elderly (126). Thus, the maintenance digoxin dose is lower in older versus younger HF patients; 0.125 mg/day is appropriate for most older patients without significant renal dysfunction. Serum levels of digoxin need only be obtained when toxicity is suspected. In the DIG trial, hospitalization for suspected digitalis toxicity increased progressively with age from 0.7% in patients 50 to 59 years old to 4.4% in those aged 80 years and older (124). Treatment of digitalis toxicity is similar regardless of age.

Other Inotropes

Although several oral phosphodiesterase inhibitors, including amrinone, milrinone, and vesnarinone initially showed promise in HF therapy, their long-term use was associated with increased mortality (127,128); thus, none are approved for clinical use. Although, intravenous milrinone may be used to treat acute HF exacerbations resistant to conventional drugs, a randomized trial showed no significant benefit (129). In the Acute Decompensated Heart Failure(ADHERE) National Registry intravenous milrinone was associated with increased mortality compared with the synthetic natriuretic peptide
nesititide and nitroglycerin (130). The calcium-sensitizing phosphodiesterase inhibitor levosimendan was superior to placebo regarding the composite primary outcome in a recent trial but showed no long-term benefit compared to dobutamine in another study (131). No data specific to the elderly are available for these agents.

Synthetic catecholemines such as dobutamine or dopamine may also be used to treat refractory HF symptoms. In a small study of patients in an intensive care setting, Rich and Imburgia (132) demonstrated that given infusion rates of dobutamine elicited lesser increases in cardiac output in patients older than 80 years than in younger patients, consistent with the age-associated decreased sensitivity to catecholamines that occurs in normals. These drugs are probably more likely to elicit tachyarrhythmias in the elderly. Low-dose dopamine, a renal vasodilator, improved creatinine clearance and urine output when added to intravenous bumetazide in elderly HF patients compared to bumetazide-alone (133). Intermittent intravenous infusions of inotropic drugs have been successfully used in elderly outpatients with refractory HF (134) although randomized controlled trials are lacking.

**Devices and Surgery**

The high morbidity and mortality associated with HF despite maximal medical therapy has led to the pursuit of additional interventions using devices and surgery in this population. Recent studies have shown that atrial-synchronized biventricular pacing, also known as cardiac resynchronization therapy (CRT), can improve LV function and enhance functional capacity, quality of life, and survival in HF patients with QRS prolongation greater than 120 milliseconds (135,136). Although no randomized trial has specifically addressed the role of CRT in the elderly, a consistent finding across trials has been a similar benefit in older versus younger patients. For example, in the Cardiac Resynchronization-Heart Failure (CARE-HF) trial, the primary endpoint of all-cause mortality or hospitalization for a major CV event was reduced from 55% in the control group to 39% in the CRT group and mortality was reduced from 30% to 20% (136). No difference in the effect of CRT on the primary outcome was found in patients older versus younger than the mean age of 66 years. An observational study comparing the effectiveness of CRT in patients younger than 70 years versus those older than 70 years found favorable responses in 75% of the younger group and 78% of the elderly (137). Survival at one year was also similar between the groups. Thus, CRT is considered a class-I indication in patients with systolic HF, a QRS duration greater than 120 milliseconds, and NYHA class III or IV symptoms, despite optimal medical therapy (107).

Given the nearly exponential increase in the risk of sudden cardiac death as LVEF decreases below 30%, it is not surprising that several studies have shown a benefit of an implantable cardioverter defibrillator (ICD) in patients with systolic HF. The Multicenter Automatic Defibrillator Implantation Trial (MADIT II) study demonstrated that prophylactic implantation of an ICD in patients with a prior myocardial infarction and ejection fraction of less than 0.3 reduced all-cause mortality from 20% to 14% over a 20-month mean follow-up (138). The benefit in patients aged 70 years and older was similar to that in younger individuals. Although HF was not required for study entry, approximately 75% of patients were receiving diuretics, presumably for HF.

More specific to the HF population, the Sudden Cardiac Death in Heart Failure Trial (SCD-HFT) found that an ICD reduced total mortality by 33% over a 45.5-month median follow-up compared with standard care in patients with systolic HF whether of ischemic or nonischemic etiology; in contrast, amiodarone showed no benefit (139). No interaction between age and ICD benefit was shown in this trial, though the mortality hazard ratio for
ICD versus placebo was somewhat more favorable among patients younger than 65 years versus older patients, 0.68 [95% confidence interval (CI) 0.50–0.93] versus 0.86 (95% CI 0.62–1.18), respectively. A similar benefit of ICDs on sudden cardiac death in patients with HF exclusively due to non-ischemic cause was found in the Defibrillators in Non-Ischemic Cardiomyopathy Treatment Evaluation (DEFINITE) trial; patients older than 65 years derived a similar benefit to younger patients (140). Of note, no additional benefit of ICDs over CRT alone on the primary endpoint of time to death or all-cause hospitalization was seen in the Comparison of Medical Therapy, Pacing, and Defibrillation in Heart Failure (COMPANION) study; CRT with or without an ICD reduced this risk by approximately 20% with similar benefits in patients older than 65 years versus younger patients (141).

Selected older patients with HF may derive major benefits from cardiac surgery. Indeed, aortic valve replacement is the treatment of choice for elderly individuals with HF secondary to calcific aortic stenosis and may be accomplished with a mortality of less than 10% in octogenarians (142,143). Coronary revascularization may ameliorate HF symptoms in selected elderly HF patients with substantial amounts of viable but ischemic myocardium due to coronary artery disease (144). Various surgical procedures, such as LV aneurysmectomy and partial left ventriculectomy, have been developed to excise nonfunctional myocardium, thereby reducing LV size, in patients with HF due to coronary artery disease. Although several studies have suggested improved clinical status and hemodynamics after these procedures, the lack of randomized controlled studies and the small number of elderly patients included prevent firm conclusions about their efficacy in this age group.

Cardiac transplantation has been successfully employed to treat end-stage HF in carefully selected patients in their seventh decade. In one such series, the one-year actuarial survival was 84%, only 4% developed a serious infection, and the incidence of rejection was 2.2 episodes per patient (145). These results compared favorably with those in younger individuals. Nevertheless, the shortage of donors and the high likelihood of medical contraindications, such as intrinsic renal or cerebrovascular disease in this age group, markedly limit the applicability of cardiac transplantation in the elderly. A promising therapy in such end-stage older HF patients is the implantation of a permanent LV assist device. Although used initially as a temporary bridge for patients undergoing cardiac transplantation, these devices have been used increasingly for long-term use in patients who are not transplant candidates (146). In a landmark multicenter trial of 129 patients (mean age 67 years) with end-stage HF, one-year survival was 52% in those receiving the LV assist device versus 25% in the controls; quality of life and mobility were also improved by the assist device (147).

**PHARMACOTHERAPY FOR HF WITH NORMAL EJECTION FRACTION**

The literature base regarding therapy of HFNEF is relatively sparse (148), in stark contrast to systolic HF, in which numerous studies over the past 30 years have generated data for evidence-based treatment of HFNEF (107,148). This situation is incongruous with the high prevalence, substantial morbidity, and significant mortality of HFNEF (149). Given the relative paucity of data, therapy is often largely empiric (148). If one considers the remarkable paradoxes encountered on the journey to evidence-based therapy for systolic HF during the past three decades (recall early opinions regarding inotropes, vasodilators, and β blockers), one may anticipate potential surprises in store as we develop the trial-based evidence needed to guide HFNEF therapy. Advances in therapy of HFNEF have been hindered by: lack of standard case definition; absence of a readily
available, reliable test that characterizes and quantitates diastolic function; and relatively poor understanding of the pathophysiology of HFNEF (46,148).

General Approach
The general approaches discussed above for systolic HF are usually applicable to HFNEF (107). There should be a search for a primary etiology. Most such patients will be found to have prominent underlying hypertension (6,8,9). A noninvasive stress test or coronary angiography is warranted in selected patients with chest pain and/or “flash pulmonary edema” to exclude severe CHD since ischemia is not only a therapeutic target in its own right but also strongly impairs diastolic relaxation. Occasional patients will be found to have hypertrophic cardiomyopathy (150,151) with or without dynamic obstruction, undiagnosed valvular or coronary disease, or, occasionally, amyloid heart disease (152). In addition, each of these underlying etiologies has specific prognostic and therapeutic implications that supersede whatever concomitant diastolic dysfunction is present.

The preceding discussion of HF pathophysiology suggests that control of hypertension is an important strategy for HFNEF. Chronic hypertension causes LVH and fibrosis, which impair diastolic chamber compliance. Acute hypertension significantly impairs diastolic relaxation. Several large studies indicate that therapy of chronic, mild systolic hypertension in the elderly is a potent means of preventing the development of HF, and it is likely that a major portion of cases prevented are due to HFNEF (153–157). Further, most patients with this disorder have fewer symptoms and repeat HF exacerbations when blood pressure is well controlled. Although not specifically designed to address this issue, data available from large studies in elderly hypertensives suggest there may be differences between classes of agents for preventing HF. For instance, the Swedish Trial in Old Patients with Hypertension (STOP)-2 trial in elderly (aged 70–84 years) mildly favored ACE inhibitors (158). Reports from the very large Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT) study which focused specifically on older patients with mild-to-moderate hypertension showed that, contrary to conventional wisdom, the diuretic chlorthalidone was superior to the α-adrenergic antagonist doxazosin (159) and was at least equivalent to ACE inhibitors and calcium antagonists for prevention of HF (160). Both chlorthalidone and hydrochlorothiazide are generic and inexpensive. A paradox is that, while chlorthalidone has been used in several large hypertension trials with hard outcome data and has been well tolerated, its use in the United States is relatively uncommon compared with hydrochlorothiazide, for which there is relatively little clinical trial data.

Because loss of atrial contraction impairs LV filling, sinus rhythm should be achieved and maintained, though this can be difficult in the elderly where the rate of atrial fibrillation is high (107). A more modest goal of rate control can also be beneficial.

SPECIFIC PHARMACOLOGICAL THERAPY
Given the paucity of data from large definitive trials, recommendations regarding specific agents are considerably less firm than for systolic HF; thus, therapy is largely empiric.

Diuretics
As for systolic HF as discussed above, while powerful loop diuretics are indispensable for rapid resolution of symptoms due to edema and pulmonary congestion, for chronic
treatment the lowest possible dose should be employed and many patients with mild or early HF can be managed with as-needed diuretics. A recent propensity analysis of nearly 7800 HF patients raised further concerns regarding increased long-term mortality and hospitalization rates attributable to diuretics in patients with HFNEF as well as in systolic HF (161).

**Digoxin**

Although most patients in the DIG trial had systolic HF, there was a sizable subgroup of 988 study subjects who had relatively preserved systolic function (ejection fraction >45%). Ahmed et al. (162) recently reported results from this important subset. They found a trend toward reduced hospitalizations for recurrent HF, which was countered by a trend toward increased hospitalizations for unstable angina. There was no effect on overall mortality or cause-specific mortality (Fig. 10) (162). Overall, there was no net effect of digoxin on hard endpoints in patients with HFNEF. However, this report did establish that there was no net harm to patients with this disorder, contrary to early reports with small numbers of subjects.

**ACE Inhibitors**

Several lines of evidence suggest that angiotensin-II antagonism, whether with ACE inhibitors or with ARBs, may be effective therapy for patients with diastolic HF. First, they are the cornerstone of systolic HF therapy, and reduce mortality and hospital admissions, and improve exercise tolerance and symptoms. Second, they interfere with the increased neurohormonal activation that is thought to be pivotal to the HF state, and as discussed above, is present in patients with diastolic HF (43,59). Third, they control hypertension and reduced LVH, reduced myocardial fibrosis, and improve LV relaxation and aortic distensibility (163–166).

In a group of elderly (mean age 80) patients with NYHA class III HF patients and presumed diastolic dysfunction (ejection fraction >50%), Aronow et al. (167) showed that enalapril significantly improved functional class, exercise duration, ejection fraction,
diastolic filling, and LV mass. In an observational study of 1402 patients, ACE inhibitor use in diastolic HF patients was associated with substantially reduced all-cause mortality (odds ratio 0.61) and HF death (odds ratio 0.55) (168). However, another study from a large database of hospitalized elderly HF patients with relatively preserved ejection fractions suggested increased mortality in patients treated with ACE inhibitors (169). The ultimate role of ACE inhibitors in HFNEF will, of course, come from appropriately powered randomized, controlled trials. The European trial Perindopril for Elderly People with Chronic Heart Failure (PEP-CHF) was designed to assess the effect of the ACE inhibitor perindopril on death, HF admission, quality of life, and six-minute walk distance in elderly (age over 70 years) HF patients with a LVEF 45% or more (170). At one-year follow-up, there was a strong trend toward reduction in the primary outcome of combined time to death or unplanned hospitalization; however, at three-year follow-up there was no difference from those initially assigned to placebo, possibly due to considerable crossover in treatment and lack of statistical power (total of only 850 patients) (171).

Angiotensin-Receptor Blockers

In a blinded, randomized, controlled, crossover trial of 20 older patients with diastolic dysfunction and an exaggerated blood pressure response to exercise, the ARB losartan improved exercise capacity and quality of life and reduced exercise systolic and pulse pressure (172). The CHARM-Preserved trial assessed the effect of candesartan on death and hospital admission in HF patients with ejection fraction greater than 40%, including a substantial number of women and elderly (173). Over a median follow-up of 36 months, CV deaths in the candesartan group did not differ significantly from placebo; however, fewer patients in the candesartan group than in the placebo group (230 vs. 279, \( p = 0.017 \)) were admitted to the hospital for HF exacerbations.

The I-PRESERVE trial is a large, multicenter, multi-national study assessing the effect of the ARB irbesartan on all-cause mortality and CV morbidity in patients with well-defined HFNEF. This trial was designed to include a more stringently defined group of HFNEF patients and utilized a higher ejection fraction, other echocardiographic characteristics, and more rigidly defined definition of HF. In addition, the sample size and duration of follow-up were modified following the report of CHARM-Preserved results. Recruitment has been completed. There are several substudies, including echocardiography, biomarkers of HF severity and of myocardial fibrosis. Follow-up is scheduled for completion in 2008.

Calcium Channel Antagonists

Setaro et al. (174) examined the role of verapamil in 22 elderly men with HF and ejection fraction greater than 45% in a randomized, double-blind, placebo-controlled crossover trial. There was a 33% improvement in exercise time and significant improvements in HF score and peak filling rate in the absence of a significant difference in blood pressure and ejection fraction. Verapamil has also been shown to improve diastolic function, symptoms, and exercise capacity in patients with hypertrophic cardiomyopathy (175–178). In animal models dihydropyridines prevent ischemia-induced increases in LV diastolic stiffness (179) and improve diastolic performance in pacing-induced HF (180,181). However, negative inotropic calcium antagonists impair early relaxation and have generally shown a tendency toward adverse outcome in patients with systolic HF (182–184).

In a randomized, crossover, blinded trial in 20 patients with diastolic dysfunction without clinical HF, Little et al. (185) compared the calcium channel antagonist verapamil
to the angiotensin-receptor antagonist candesartan with the outcomes of peak exercise blood pressure, exercise time and quality of life (18). Whereas both agents blunted the peak SBP response to exercise, only candesartan improved exercise time and quality of life (Fig. 11) (185).

**β Adrenergic Blockers**

β Adrenergic blockers substantially improve mortality in systolic HF patients, regress left ventricular hypertrophy, increase the ischemic threshold, and increase the time for diastolic filling, all portending potential benefit in diastolic HF. On the other hand, Cheng et al. (186) and others have shown that early diastolic relaxation is impaired by β-adrenergic blockade. The role of β blockers, like ACE inhibitors and calcium channel antagonists in HFNEF, will only be revealed when the results of well-designed large clinical trials are available. A significant percentage of older patients have relative contraindications to β blockers.

In the previously mentioned SENIORS trial of the β-1-selective blocker nebivolol in older patients with symptomatic HF or an ejection fraction less than 35%, about 25% (475) of the participants had an ejection fraction of greater than 45% at the time of randomization (122). Although the authors concluded that nebivolol was effective regardless of ejection fraction, the relatively modest effect on outcomes compared to other β blockers has raised questions (187). Further, the published data to date lacks important detail regarding those patients with relatively preserved ejection fraction.

**Aldosterone Antagonists**

There are multiple lines of evidence to suggest the potential for benefit from antagonism of aldosterone in patients with HFNEF (188). Aldosterone is a potent promoter of myocardial hypertrophy and fibrosis, both of which are thought to be key pathophysiolgies of the majority of HFNEF patients. In a subset analysis of the RALES trial, most of the survival improvement imparted by spironolactone appeared to occur in patients with the highest baseline concentrations of procollagen biomarkers of fibrosis, and these were reduced with chronic therapy (189). Aldosterone antagonism also has potential benefits for improvement in vascular fibrosis and stiffness. A placebo-controlled study of 30 patients with hypertension, dyspnea on exertion, and delayed
relaxation LV filling pattern by Doppler showed that strain rate and peak strain improved with spironolactone therapy aldosterone antagonism (190). Spironolactone is much better tolerated in women, who have lower rates of mastodynia than men. On the basis of these and other data, a large, National Institutes of Health funded, randomized, placebo-controlled, multicenter, multinational trial of spironolactone, called Treatment of Preserved Cardiac Function Heart Failure with an Aldosterone Antagonist (TOPCAT), is being conducted.

**Collagen Cross-Link Breakers**

Collagen cross-links increase with aging and diabetes, and cause increased vascular and myocardial stiffness. Alagebrum, a novel cross-link breaker, improved vascular and LV stiffness in dogs. Little et al. reported results of a small, open label, four-month trial of this agent in elderly patients (191). LV mass, quality of life, and tissue Doppler diastolic function indexes improved, but there were no significant improvements in exercise capacity or aortic distensibility, the primary outcomes of the trial (191).

**Endothelin-Receptor Antagonists**

Endothelin is a potent arterial vasoconstrictor that also depresses diastolic as well as systolic dysfunction (192). An ongoing trial is assessing the potential for the endothelin-receptor antagonist sixtasentan to improve exercise time.

**Future Studies**

Given the importance of the syndrome and the paucity of treatment trials, this will likely be an area of substantial research activity for many years. On the basis of pathophysiological insights discussed above, future studies might assess physiological pacing in subsets with chronotropic incompetence, mitigation of anemia, improvement in glycemic control, weight loss, exercise training, and novel pharmacological agents.

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Supraventricular Tachyarrhythmias in the Elderly

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ATRIAL FIBRILLATION

Atrial fibrillation (AF) is a cardiac rhythm which has irregular undulations of the baseline electrocardiogram (ECG) of varying amplitude, contour, and spacing known as fibrillation waves, with the atrial rate between 350 and 600 beats per minute. The fibrillatory waves are seen best in leads V1, II, III, and a ventricular fibrillation (VF). The fibrillation waves may be large and coarse, or they may be fine with an almost flat ECG baseline. The ventricular rate in AF is irregular unless complete atrioventricular (AV) block or dissociation is present. The contour of the QRS complex in AF is normal unless there is prior bundle branch block, an intraventricular conduction defect, or aberrant ventricular conduction.

If AF is associated with a slow regular ventricular response, there is complete AV block with an AV junctional escape rhythm or idioventricular escape rhythm. Myocardial infarction, degenerative changes in the conduction system, and drug toxicity such as digitalis toxicity are major causes of complete AV block. If AF is associated with a regular ventricular response between 60 and 130 beats per minute, there may be complete AV dissociation with an accelerated AV junctional rhythm caused by an acute inferior myocardial infarction, digitalis toxicity, open heart surgery, or myocarditis, usually rheumatic. Regularization of the ventricular response in AF may also occur in patients with complete AV dissociation due to ventricular tachycardia or a ventricular paced rhythm.

Prevalence

AF is the most common sustained cardiac arrhythmia. The prevalence of AF increases with age (1–5). In the Framingham Study, the prevalence of chronic AF was 2% in persons aged 60 to 69 years, 5% in persons aged 70 to 79 years, and 9% in persons aged 80 to 89 years (1). In a study of 2101 persons, mean age 81 years, the prevalence of
chronic AF was 5% in persons aged 60 to 70 years, 13% in persons aged 71 to 90 years, and 22% in persons aged 91 to 103 years (2). Chronic AF was present in 16% of 1160 men, mean age 80 years, and in 13% of 2464 women, mean age 81 years (3). In 5201 persons aged 65 years and older in the Cardiovascular Health Study, the prevalence of AF was 6% in men and 5% in women (4). In 1563 persons, mean age 80 years, living in the community, the prevalence of chronic AF was 9% (5). In the Cardiovascular Health Study, the incidence of AF was 19.2 per 1000 person-years (6).

AF may be paroxysmal or chronic. Episodes of paroxysmal AF may last from a few seconds to several weeks. Sixty-eight percent of persons presenting with AF of less than 72 hours’ duration spontaneously converted to sinus rhythm (7).

Predisposing Factors

Multiple, small reentrant circuits arising in the atria, exhibiting variable wave lengths, colliding, being extinguished, and arising again usually cause AF (8). Rapidly firing foci are commonly located in or near the pulmonary veins and may also cause AF (9). Factors responsible for onset of AF include triggers that induce the arrhythmia and the substrate that sustains it. Atrial inflammation or fibrosis acts as a substrate for the development of AF. Triggers of AF include acute atrial stretch, accessory AV pathways, premature atrial beats or atrial tachycardia, sympathetic or parasympathetic stimulation, and ectopic foci occurring in sleeves of atrial tissue within the pulmonary veins or vena caval junctions (10). Predisposing factors for AF include age, alcohol, aortic regurgitation and stenosis, atrial septal defect, autonomic dysfunction, cardiac or thoracic surgery, cardiomyopathies, chronic lung disease, cocaine, congenital heart disease, coronary heart disease, congestive heart failure (CHF), diabetes mellitus, drugs (especially sympathomimetics), emotional stress, excessive coffee, hypertension, hyperthyroidism, hypoglycemia, hypokalemia, hypovolemia, hypoxia, left atrial enlargement, left ventricular (LV) dysfunction, LV hypertrophy (LVH), male gender, mitral annular calcium (MAC), mitral stenosis and regurgitation, myocardial infarction (MI), myocarditis, neoplastic disease, obesity, pericarditis, pneumonia, pulmonary embolism, rheumatic heart disease, sick sinus syndrome, smoking, systemic infection, and the Wolff-Parkinson-White (WPW) syndrome.

In 254 older persons with AF compared with 1445 older persons with sinus rhythm, mean age 81 years, two-dimensional (2D) and Doppler echocardiography showed that the prevalence of AF was increased 17.1 times by rheumatic mitral stenosis, 2.9 times by left atrial enlargement, 2.5 times by abnormal LV ejection fraction, 2.3 times by aortic stenosis, 2.2 times by MAC and by greater than or equal to 1 + mitral regurgitation, 2.1 times by greater than or equal to 1 + aortic regurgitation, and 2.0 times by LVH (11). The Framingham Study demonstrated that low serum thyrotropin levels were independently associated with a 3.1 times increase in the development of new AF in older patients (12).

Numerous drugs can induce AF (13). A meta-analysis of 11 studies including 56,308 patients showed that angiotensin-converting enzyme inhibitors and angiotensin receptor blockers significantly reduced the risk of AF by 28%, with a 44% significant reduction in AF in patients with CHF (14). This benefit was limited to patients with reduced LV ejection fraction (LVEF) or LVH (14).

Associated Risks

In the Framingham Study, the incidence of death from cardiovascular causes was 2.7 times higher in women and 2.0 times higher in men with chronic AF, than in women and men with sinus rhythm (15). The Framingham Study also found that after adjustment for
preexisting cardiovascular conditions, the odds ratio for mortality in persons with AF was 1.9 in women and 1.5 in men (16). At 42-month follow-up of 1359 persons with heart disease, mean age 81 years, patients with chronic AF had a 2.2 times increased risk of having new coronary events than patients with sinus rhythm, after controlling for other prognostic variables (17). In the Copenhagen City Heart Study, the effect of AF on the risk of cardiovascular death was significantly increased 4.4 times in women and 2.2 times in men (18).

AF was present in 22% of 106,780 persons aged 65 years or older with acute MI in the Cooperative Cardiovascular Project (19). Compared with sinus rhythm, patients with AF had a higher in-hospital mortality (25% vs. 16%), 30-day mortality (29% vs. 19%), and one-year mortality (48% vs. 33%) (19). AF was an independent predictor of in-hospital mortality (odds ratio = 1.2), 30-day mortality (odds ratio = 1.2), and one-year mortality (odds ratio = 1.3) (19). Older patients developing AF during hospitalization had a worse prognosis than older patients presenting with AF (19). In the Global Use of Strategies to Open Occluded Coronary Arteries (GUSTO-III) study, 906 of 13,858 patients (7%) developed AF during hospitalization (20). After adjusting for baseline differences, AF increased the 30-day mortality (odds ratio = 1.6) and the one-year mortality (odds ratio = 1.6) (20).

In the Platelet Glycoprotein IIb/IIIa in Unstable Angina: Receptors Suppression Using Integrilin Therapy (PURSUIT) trial, AF developed in 6.4% of 9432 patients with acute coronary syndromes without ST-segment elevation (21). After adjustment for other variables, patients with AF had a higher 30-day mortality (hazard ratio = 4.0) and six-month mortality (hazard ratio = 3.0) than patients without AF (21).

AF is also an independent risk factor for stroke, especially in older persons (1,2). In the Framingham Study, the relative risk of stroke in patients with nonvalvular AF compared with patients with sinus rhythm was increased 2.6 times in patients aged 60 to 69 years, increased 3.3 times in patients aged 70 to 79 years, and increased 4.5 times in patients aged 80 to 89 years (1). Chronic AF was an independent risk factor for thromboembolic (TE) stroke with a relative risk of 3.3 in 2101 persons, mean age 81 years (2). The three-year incidence of TE stroke was 38% in older persons with chronic AF and 11% in older persons with sinus rhythm (2). The five-year incidence of TE stroke was 72% in older persons with AF and 24% in older persons with sinus rhythm (2). At 37-month follow-up of 1476 patients who had 24-hour ambulatory ECGs (AECGs), the incidence of TE stroke was 43% for 201 patients with AF (relative risk = 3.3), 17% for 493 patients with paroxysmal supraventricular tachycardia, and 18% for 782 patients with sinus rhythm (22).

In the Copenhagen City Heart Study, the effect of AF on the risk of stroke was significantly increased 7.6 times in women and 1.7 times in men (18). AF is also a risk factor for impaired cognitive function (23).

In 2384 persons, mean age 81 years, AF was present in 17% of older persons with LVH and in 8% of persons without LVH (24). Both AF (risk ratio = 3.2) and LVH (risk ratio = 2.8) were independent risk factors for new TE stroke at 44-month follow-up (24). The higher prevalence of LVH in older patients with chronic AF contributes to the increased incidence of TE stroke in older patients with AF.

Both AF (risk ratio = 3.3) and 40% to 100% extracranial carotid arterial disease (ECAD) (risk ratio = 2.5) were independent risk factors for new TE stroke at 45-month follow-up of 1846 persons, mean age 81 years (25). Older persons with both chronic AF and 40% to 100% ECAD had a 6.9 times higher probability of developing new TE stroke than older persons with sinus rhythm and no significant ECAD (25).

Cerebral infarctions were demonstrated in 22% of 54 autopsied patients aged 70 or older with paroxysmal AF (26). Symptomatic cerebral infarction was 2.4 times more
common in older patients with paroxysmal AF, than in older patients with sinus rhythm (26). AF also causes silent cerebral infarction (27).

AF predisposes to CHF in older patients. As much as 30% to 40% of LV end-diastolic volume may be attributable to left atrial contraction in older persons. Absence of a coordinated left atrial contraction reduces late diastolic filling of the LV because of loss of the atrial kick. In addition, a fast ventricular rate in AF shortens the LV diastolic filling period, further reducing LV filling and stroke volume.

A retrospective analysis of the Studies of Left Ventricular Dysfunction Prevention and Treatment Trials demonstrated that AF was an independent risk factor for all-cause mortality (relative risk = 1.3), progressive pump failure (relative risk = 1.4), and death or hospitalization for CHF (relative risk = 1.3) (28). AF was present in 37% of 355 patients, mean age 80 years, with prior MI, CHF, and abnormal LVEF and in 33% of 296 patients, mean age 82 years, with prior MI, CHF, and normal LVEF (29). In this study, AF was an independent risk factor for mortality with a risk ratio of 1.5 (29).

A fast ventricular rate associated with chronic or paroxysmal AF may cause a tachycardia-related cardiomyopathy, which may be an unrecognized but curable cause of CHF (30,31). Slowing the rapid ventricular rate by radiofrequency ablation of the AV node with permanent pacing caused an improvement in LVEF in patients with medically refractory AF (32). In a substudy of the Ablate and Pace Trial, 63 of 161 patients (39%) with AF referred for AV junction ablation and right ventricular pacing had an abnormal LVEF (33). Forty-eight of the 63 patients had follow-up echocardiograms. Sixteen of the 48 patients (33%) had a marked improvement in LVEF to a value more than 45% after ventricular rate control by AV junction ablation (33).

Clinical Symptoms

Patients with AF may be symptomatic or asymptomatic with their arrhythmia diagnosed by physical examination or by an ECG. Examination of a patient after a stroke may lead to the diagnosis of AF. Symptoms caused by AF may include palpitations, skips in heartbeat, exercise intolerance, fatigue on exertion, cough, chest pain, dizziness, and syncope. A rapid ventricular rate and loss of atrial contraction decrease cardiac output and may lead to angina pectoris, CHF, hypotension, acute pulmonary edema, and syncope, especially in patients with aortic stenosis, mitral stenosis, or hypertrophic cardiomyopathy.

Diagnostic Tests

When AF is suspected, a 12-lead ECG with a one-minute rhythm strip should be obtained to confirm the diagnosis. If paroxysmal AF is suspected, a 24-hour AECG should be obtained. All patients with AF should have an M-mode, 2D, and Doppler echocardiogram to determine the presence and severity of the cardiac abnormalities causing AF and to identify risk factors for stroke. Appropriate tests for noncardiac causes of AF should be obtained when clinically indicated. Thyroid function tests should be obtained, as AF or CHF may be the only clinical manifestations of apathetic hyperthyroidism in older patients.

Treatment of Underlying Causes

Management of AF should include therapy of the underlying disease (such as hyperthyroidism, pneumonia, or pulmonary embolism) when possible. Surgical candidates for mitral valve replacement should have mitral valve surgery if it is clinically indicated. If mitral valve surgery is not performed in patients with significant mitral valve
disease, elective cardioversion should not be attempted in patients with AF since early frequent relapses are common if AF converts to sinus rhythm. Precipitating factors such as CHF, infection, hypoglycemia, hypokalemia, hypovolemia, and hypoxia should be treated immediately. Alcohol, coffee, and drugs (especially sympathomimetics) that precipitate AF should be avoided. Paroxysmal AF associated with the tachycardia-bradycardia (sick sinus syndrome) should be treated with permanent pacing in combination with drugs to decrease a rapid ventricular rate associated with AF (34).

**Control of Very Rapid Ventricular Rate**

Direct-current (DC) cardioversion should be performed immediately in patients who have paroxysmal AF with a very fast ventricular rate associated with an acute MI, chest pain caused by myocardial ischemia, hypotension, severe CHF, syncope, or pre-excitation syndromes. Intravenous β blockers (35–38), diltiazem (39), or verapamil (40) may be used to reduce immediately a very rapid ventricular rate associated with AF except in patients with pre-excitation syndromes.

Propranolol should be given intravenously in a dose of 1.0 mg over a five-minute period and then administered intravenously at a rate of 0.5 mg/min to a maximum dose of 0.1 mg/kg. Esmolol administered intravenously in a dose of 0.5 mg/kg over one minute followed by 0.05 to 0.1 mg/kg per minute may also be used to decrease a very rapid ventricular rate in AF. After the very rapid ventricular rate is reduced, oral propranolol should be started with an initial dose of 10 mg given every six hours. This dose may be increased progressively to a maximum dose of 80 mg every six hours if necessary. Other β blockers can be used with appropriate doses administered.

The initial dose of diltiazem administered intravenously to slowdown a very rapid ventricular rate in AF is 0.25 mg/kg given over two minutes. If this dose does not slow down the very fast ventricular rate or cause adverse effects, a second dose of 0.35 mg/kg administered intravenously over two minutes should be given 15 minutes after the first dose. After slowing down the very fast ventricular rate, oral diltiazem should be started with an initial dose of 60 mg given every six hours. If necessary, this dose may be increased to a maximum dose of 90 mg every six hours.

The initial dose of verapamil given intravenously is 0.075 mg/kg (to a maximum dose of 5 mg). If this dose does not decrease the very rapid ventricular rate or cause adverse effects, a second dose of 0.075 mg/kg (to a maximum dose of 5 mg) should be administered intravenously 10 minutes after the first dose. If the second dose of intravenous verapamil does not decrease the very rapid ventricular rate or cause adverse effects, a dose of 0.15 mg/kg (to a maximum dose of 10 mg) should be administered intravenously 30 minutes after the second dose. After slowing the very rapid ventricular rate, oral verapamil should be started with an initial dose of 80 mg every six to eight hours. This dose may be increased to 120 mg every six hours over the next two to three days.

**Control of Rapid Ventricular Rate**

Digitalis glycosides are ineffective in converting AF to sinus rhythm (41). Digoxin is also ineffective in decreasing a rapid ventricular rate in AF if there is associated fever, hyperthyroidism, acute blood loss, hypoxia, or any condition involving increased sympathetic tone (42). However, digoxin should be used to decrease a rapid ventricular rate in AF unassociated with increased sympathetic tone, hypertrophic cardiomyopathy, or the WPW syndrome, especially if there is LV systolic dysfunction.
The usual initial dose of digoxin administered to undigitalized patients with AF is 0.5 mg orally. Depending on the clinical response, a second oral dose of 0.25 mg may be given in six to eight hours, and a third oral dose of 0.25 mg may be given in another six to eight hours to slow down a rapid ventricular rate. The usual maintenance oral dose of digoxin given to patients with AF is 0.25 to 0.5 mg daily, with the dose reduced to 0.125 to 0.25 mg daily for older patients who are more susceptible to digitalis toxicity (43).

Oral β blockers (44), diltiazem (45), or verapamil (46) should be added to the therapeutic regimen if a rapid ventricular rate in AF occurs at rest or during exercise, despite digoxin. These drugs act synergistically with digoxin to depress conduction through the AV junction. In a study of atenolol 50 mg daily, digoxin 0.25 mg daily, diltiazem-CD 240 mg daily, digoxin 0.25 mg plus atenolol 50 mg daily, and digoxin 0.25 mg plus diltiazem-CD 240 mg daily, digoxin and diltiazem as single drugs were least effective and digoxin plus atenolol was most effective in controlling the ventricular rate in AF during daily activities (47).

Amiodarone is the most effective drug for reducing a rapid ventricular rate in AF (48,49). The noncompetitive β-receptor inhibition and calcium channel blockade are powerful AV nodal conduction depressants. However, the adverse side effect profile of amiodarone limits its use in the treatment of AF. Oral doses of 200 mg to 400 mg of amiodarone daily may be given to selected patients with symptomatic life-threatening AF refractory to other drugs.

Therapeutic concentrations of digoxin do not decrease the frequency of episodes of paroxysmal AF, or the duration of episodes of paroxysmal AF diagnosed by 24-hour AECGS (50,51). Digoxin has been shown to increase the duration of episodes of paroxysmal AF, a result consistent with its action in reducing the atrial refractory period (50). Therapeutic concentrations of digoxin also do not prevent a fast ventricular rate from developing in patients with paroxysmal AF (50–52). After a brief episode of AF, digoxin increases the shortening that occurs in atrial refactoriness and predisposes to the reinduction of AF (53). Therefore, digoxin should be avoided in patients with sinus rhythm with a history of paroxysmal AF.

**Nondrug Therapies**

Radiofrequency catheter modification of AV conduction should be performed in patients with symptomatic AF in whom a rapid ventricular rate cannot be decreased by drugs (54,55). If this procedure does not control the fast ventricular rate associated with AF, complete AV block produced by radiofrequency catheter ablation followed by permanent pacemaker implantation should be performed (56). In a randomized controlled study of 66 persons with CHF and chronic AF, AV junction ablation with implantation of a ventricular demand pacemaker with rate modulation was superior to drug treatment in controlling symptoms (57). Long-term survival is similar for patients with AF whether they receive radiofrequency ablation of the AV node and implantation of a permanent pacemaker, or drug therapy (58). In 44 patients, mean age 78 ± 5 years, radiofrequency catheter ablation followed by pacemaker implantation was successful in ablating the AV junction in 43 of 44 patients (98%), with AF and a rapid ventricular rate not controlled by drug therapy (59).

Surgical techniques have been developed for use in patients with AF in whom the ventricular rate cannot be decreased by drug treatment (60,61). The maze procedure is a surgical dissection of the right and left atrium creating a maze through which the electrical activation is compartmentalized, preventing the formation and perpetuation of the multiple wavelets needed for maintenance of AF. This procedure is typically performed in association with mitral valve surgery or coronary artery bypass surgery (CABS). At two-
three-year follow-up, 74% of 39 patients and 90% of 100 patients undergoing the maze procedure remained in sinus rhythm (62,63). Thirty-five of 43 patients (85%) with drug-refractory, lone paroxysmal AF were arrhythmia free after maze surgery (64). At 29-month follow-up, 18 of 28 patients (64%), mean age 71 years, who had an intraoperative radiofrequency maze procedure for treating AF at the time of valve surgery or CABS were in sinus rhythm (65).

Another intraoperative approach for treating AF in patients undergoing mitral valve surgery is cryoablation limited to the posterior left atrium. Sinus rhythm was restored in 20 of 29 patients (69%) with chronic AF undergoing this procedure (66).

Ablation of pulmonary vein foci that cause AF is a developing area in the treatment of AF. However, recurrent AF develops in 40% to 60% of patients despite initial efficacy with this procedure (67). Another problem with this approach is a 3% incidence of pulmonary vein stenosis occurring after this procedure (67).

Recent randomized studies demonstrated that circumferential pulmonary vein radiofrequency ablation was significantly more effective than antiarrhythmic drug therapy in preventing recurrence of AF (93% vs. 35%) in 198 patients at one year (68), and (87% vs. 37%) in 67 patients at one year (69). There are no long-term follow-up data showing a reduction in stroke risk in patients apparently cured of AF with radiofrequency catheter ablation.

Modification of the substrate responsible for AF can be accomplished in the right or left atrium with linear lesions. This catheter maze–ablation approach is effective in a small percentage of patients (70).

The Atrioverter, an implantable defibrillator connected to right atrial and right coronary sinus defibrillation leads, causes restoration of sinus rhythm by low-energy shock and has an 80% efficacy in terminating AF (71). Further efforts are needed to improve patient tolerability and to prevent earlier recurrence of AF after successful transvenous atrial defibrillation. The implanted atrial defibrillator is currently available only in combination with a ventricular defibrillator. The Atrioverter may also convert atrial tachycardia to sinus rhythm using an atrial pacing overdrive algorithm before such tachycardias induce AF.

Pacing

Paroxysmal AF associated with the tachycardia-bradycardia (sick sinus) syndrome should be treated with a permanent pacemaker combined with drugs to slow down a rapid ventricular rate associated with AF (34). Ventricular pacing is an independent risk factor for the development of chronic AF in patients with paroxysmal AF associated with the tachycardia-bradycardia syndrome (72). Patients with paroxysmal AF associated with the tachycardia-bradycardia syndrome and no signs of AV conduction abnormalities should be treated with atrial pacing or dual-chamber pacing rather than with ventricular pacing because atrial pacing is associated with less AF, fewer TE complications, and a lower risk of AV block than is ventricular pacing (73).

Many older patients are able to tolerate AF without the need for therapy because the ventricular rate is slow because of concomitant AV nodal disease. These patients should not be treated with drugs that depress AV conduction. A permanent pacemaker should be implanted in patients with AF who develop cerebral symptoms such as dizziness or syncope associated with ventricular pauses longer than three seconds, which are not drug-induced, as documented by a 24-hour AECG (74). If patients with AF have drug-induced symptomatic bradycardia and the causative drug cannot be discontinued, a permanent pacemaker must be implanted.
Atrial pacing is effective in treating vagotonic AF (75), and may be considered if treatment with a vagolytic antiarrhythmic drug such as disopyramide is ineffective. Atrial pacing is also effective in treating patients with the sick sinus syndrome (73). However, when bradycardia is not an indication for pacing, atrial-based pacing may not prevent episodes of AF (76). Dual-site atrial pacing is more efficacious than single-site pacing for preventing AF (77). However, the patients in this study had a bradycardia indication for pacing and continued to need antiarrhythmic drugs (77).

Dual-site atrial pacing with continued sinus overdrive for AF in patients with bradycardia prolonged time to AF recurrence and reduced AF burden in patients with paroxysmal AF (78). However, there was no difference in AF checklist symptom scores or overall quality-of-life scores (78). The absence of an effect on symptom control suggests that pacing should be used as adjunctive therapy with other treatment modalities for AF (78).

Biatrial pacing after CABS has also been demonstrated to reduce the incidence of AF (79). All ECGs in patients with paced rhythm should be examined closely for underlying AF to prevent underrecognition of AF and undertreatment with anticoagulants (80). Permanent pacing to prevent AF is not indicated (81).

**Percutaneous Left Atrial Appendage Transcatheter Occlusion**

In two prospective multicenter trials, percutaneous left atrial appendage occlusion using the PLAATO system was attempted in 111 patients, mean age 71 years, with a contraindication to anticoagulant therapy and at least one additional risk factor for stroke (82). Implantation was successful in 108 of 111 patients (97%). At 9.8-month follow-up, two patients (2%) developed stroke (82). Long-term studies are needed to confirm the long-term safety of the device and a reduction in TE stroke.

**Wolff-Parkinson-White Syndrome**

DC cardioversion should be performed if a rapid ventricular rate in patients with paroxysmal AF associated with the WPW syndrome is life threatening or fails to respond to drug therapy. Drug treatment for paroxysmal AF associated with the WPW syndrome includes propranolol plus procainamide, disopyramide, or quinidine (83). Digoxin, diltiazem, and verapamil are contraindicated in patients with AF with the WPW syndrome because these drugs shorten the refractory period of the accessory AV pathway, resulting in more rapid conduction down the accessory pathway. This results in a marked increase in ventricular rate. Radiofrequency catheter ablation or surgical ablation of the accessory conduction pathway should be considered in patients with AF, and rapid AV conduction over the accessory pathway (84). In 500 patients with an accessory pathway, radiofrequency catheter ablation of the accessory pathway was successful in 93% of patients (85).

**Elective Cardioversion**

Elective DC cardioversion has a higher success rate than does medical cardioversion in converting AF to sinus rhythm (86). Table 1 shows favorable and unfavorable conditions for elective cardioversion of chronic AF.

The American College of Cardiology/American Heart Association/European Society for Cardiology (ACC/AHA/ESC) guidelines state that class I indications for cardioversion of AF to sinus rhythm include (1) immediate DC cardioversion in patients...
with paroxysmal AF and a rapid ventricular rate who have ECG evidence of acute MI or symptomatic hypotension, angina, or CHF that does not respond promptly to pharmacological measures and (2) DC or drug cardioversion in patients with chronic AF without hemodynamic instability when symptoms of AF are unacceptable (87).

Elective cardioversion of AF either by DC or by antiarrhythmic drugs should not be performed in asymptomatic elderly patients with chronic AF. Rectilinear, biphasic shocks have been found to have greater efficacy, and need less energy than the traditional damped sine wave monophasic shocks (88). Therefore, biphasic shocks to cardiovert AF should become the clinical standard.

Antiarrhythmic drugs that have been used to convert AF to sinus rhythm include amiodarone, disopyramide, dofetilide, encainide, flecainide, ibutilide, procainamide, propafenone, quinidine, and sotalol. None of these drugs is as successful as DC cardioversion, which has a success rate of 80% to 90% in converting AF to sinus rhythm. All of these drugs are proarrhythmic and may aggravate or cause cardiac arrhythmias.

Encainide and flecainide caused atrial proarrhythmic effects in 6 of 60 patients (10%) (89). The atrial proarrhythmic effects included conversion of AF to atrial flutter with a one-to-one AV conduction response and a very fast ventricular rate (89). Flecainide has caused ventricular tachycardia (VT) and VF in patients with chronic AF (90). Antiarrhythmic drugs including amiodarone, disopyramide, flecainide, procainamide, propafenone, quinidine, and sotalol caused cardiac adverse effects in 73 of 417 patients (18%) hospitalized for AF (91). Class IC drugs such as encainide, flecainide, and propafenone should not be used in patients with prior MI or abnormal LVEF because these drugs may cause life-threatening ventricular tachyarrhythmias in these patients (92).

Dofetilide and ibutilide are class III antiarrhythmic drugs that have been used for the conversion of AF to sinus rhythm. Eleven of 75 patients (15%) with AF treated with

### Table 1  Conditions Favorable and Unfavorable for Cardioversion of Atrial Fibrillation

<table>
<thead>
<tr>
<th>Favorable conditions</th>
<th>Unfavorable conditions</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;1-year duration of AF</td>
<td>Duration of atrial fibrillation &gt; 1 year</td>
</tr>
<tr>
<td>No or minimal cardiomegaly</td>
<td>Moderate to severe cardiomegaly</td>
</tr>
<tr>
<td>Echocardiographic left atrial dimension &lt; 45 mm</td>
<td>Echocardiographic left atrial dimension &gt; 45 mm</td>
</tr>
<tr>
<td>After treatment of a precipitating cause such as acute MI, cardiac or thoracic surgery, hyperthyroidism, pneumonia, or pericarditis</td>
<td>Digitalis toxicity (contraindicated)</td>
</tr>
<tr>
<td>After corrective valvular surgery</td>
<td>Slow ventricular rate (contraindicated)</td>
</tr>
<tr>
<td>Symptomatic AF with hemodynamic improvement and decrease in symptoms expected from sinus rhythm, especially in patients with valvular aortic stenosis or hypertrophic obstructive cardiomyopathy</td>
<td>Sick sinus syndrome (contraindicated)</td>
</tr>
<tr>
<td>Mitral valve disease</td>
<td>Chronic obstructive lung disease</td>
</tr>
<tr>
<td>Heart failure</td>
<td>Recurrent AF despite antiarrhythmic drugs</td>
</tr>
<tr>
<td>Inability to tolerate antiarrhythmic drugs</td>
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</table>

**Abbreviations:** AF, atrial fibrillation; MI, myocardial infarction.
intravenous dofetilide converted to sinus rhythm (93). Torsade de pointes occurred in 3% of patients treated with intravenous dofetilide (93). After one month, 22 of 190 patients (12%) with AF and CHF had sinus rhythm restored with dofetilide, compared to three of 201 patients (1%) treated with placebo (94). Torsade de pointes developed in 25 of 762 patients (3%) treated with dofetilide and in none of the 756 patients (0%) treated with placebo (94). Twenty-three of 79 patients (29%) with AF treated with intravenous ibutilide converted to sinus rhythm (95). Polymorphic VT developed in 4% of patients who received intravenous ibutilide in this study (95). Baseline bradycardia with AF may predispose to ibutilide-induced polymorphic VT.

DC cardioversion of AF has a higher success rate in converting AF to sinus rhythm and a lower incidence of cardiac adverse effects, than treatment with any antiarrhythmic drug. However, pretreatment with ibutilide has been found to facilitate transthoracic cardioversion of AF (96).

Unless transesophageal echocardiography has demonstrated no thrombus in the left atrial appendage before cardioversion (97), oral warfarin should be administered for three weeks before elective DC or drug conversion of patients with AF to sinus rhythm (98). Anticoagulant therapy should also be given at the time of cardioversion and continued until sinus rhythm has been maintained for four weeks (98). After DC or drug cardioversion of AF to sinus rhythm, the left atrium becomes stunned and contracts poorly for three to four weeks, predisposing to TE stroke unless the patient is maintained on oral warfarin (99,100). The maintenance dose of oral warfarin should be titrated by serial prothrombin times so that the international normalized ratio (INR) is 2.0 to 3.0 (98).

In a multicenter, randomized prospective study, 1222 patients with AF of more than two days duration were randomized to either treatment guided by the findings on transesophageal echocardiography or to management with conventional therapy (101). The primary endpoint was cerebrovascular accident, transient ischemic attack, and peripheral embolism within eight weeks. The incidence of embolic events at eight weeks was 0.8% in the transesophageal echocardiography treatment group and 0.5% in the conventional treatment group (101). At eight weeks, there were also no significant differences between the two groups in the rates of death, maintenance of sinus rhythm, or functional status (101). However, there was a trend toward a higher rate of death from any cause in the transesophageal echocardiography treatment group (2.4%) than in the conventional treatment group (1.0%) ($p = 0.06$) (101).

This study showed the importance of maintaining therapeutic anticoagulation in the period after cardioversion, even if there is no transesophageal echocardiographic evidence of thrombus (100,102). The best management strategy for patients with evidence of an atrial thrombus on initial transesophageal echocardiography remains controversial (103). In the absence of data from a randomized trial, patients probably should have follow-up transesophageal echocardiography after one month of warfarin therapy to document resolution of the atrial thrombus (103,104).

Use of Antiarrhythmic Drugs to Maintain Sinus Rhythm

The efficacy and safety of antiarrhythmic drugs after cardioversion of AF to maintain sinus rhythm has been questioned. A meta-analysis of six double-blind, placebo-controlled studies of quinidine involving 808 patients who had DC cardioversion of chronic AF to sinus rhythm demonstrated that 50% of patients treated with quinidine and 25% of patients treated with placebo remained in sinus rhythm at one-year follow-up (105). However, the mortality was significantly higher in patients treated with quinidine (2.9%) than in
patients treated with placebo (0.8%) (105). In a study of 406 patients, mean age 82 years, with heart disease and complex ventricular arrhythmias, the incidence of adverse effects causing drug cessation was 48% for quinidine and 55% for procainamide (106). The incidence of total mortality at two-year follow-up was insignificantly higher in patients treated with quinidine or procainamide compared with patients not receiving an antiarrhythmic drug (106).

In another study, 85 patients were randomized to quinidine and 98 patients to sotalol after DC cardioversion of AF to sinus rhythm (107). At six-month follow-up, 48% of quinidine-treated patients and 52% of sotalol-treated patients remained in sinus rhythm (107). At one-year follow-up of 100 patients with AF cardioverted to sinus rhythm, 37% of 50 patients randomized to sotalol and 30% of 50 patients randomized to propafenone remained in sinus rhythm (108).

In a study of 403 patients with at least one episode of AF in the prior six months, 201 patients were treated with amiodarone and 202 patients were treated with sotalol or propafenone (109). At 16-month follow-up, AF recurred in 35% of patients treated with amiodarone and in 63% of patients treated with sotalol or propafenone (109). Adverse effects causing discontinuation of drug occurred in 18% of patients treated with amiodarone and in 11% of patients treated with sotalol or propafenone (109).

After cardioversion of 394 patients with AF to sinus rhythm, 197 patients were randomized to metoprolol controlled/extended release (CR/XL) and 197 patients to placebo (110). At six-month follow-up, the percent of patients in sinus rhythm was significantly higher on metoprolol CR/XL (51%) than on placebo (40%) (110). The heart rate in patients who relapsed into AF was also significantly lower in pts treated with metoprolol CR/XL, than in patients treated with placebo (110).

In a study of 384 patients with a history of AF or atrial flutter, azimilide lengthened the median time to first symptomatic arrhythmia recurrence from 17 days in the placebo group to 60 days in the azimilide group (111). However, additional data on both efficacy and safety of azimilide are necessary before knowing its role in clinical practice.

Of the 1330 patients in the Stroke Prevention in Atrial Fibrillation (SPAF) study, 127 persons were taking quinidine, 57 procainamide, 34 flecainide, 20 encainide, 15 disopyramide, and 7 amiodarone (112). Patients who were taking an antiarrhythmic drug had a 2.7 times higher adjusted relative risk of cardiac mortality and a 2.3 times higher adjusted relative risk of arrhythmic death compared with patients not taking an antiarrhythmic drug (112). Patients with a history of CHF who were taking an antiarrhythmic drug had a 4.7 times increased risk of cardiac death and a 3.7 times increased risk of arrhythmic death than patients with a history of CHF not taking an antiarrhythmic drug (112).

A meta-analysis of 59 randomized, controlled trials comprising 23,229 patients that investigated the use of aprindine, disopyramide, encainide, flecainide, imipramine, lidocaine, mexiletine, moricizine, phenytoin, procainamide, quinidine, and tocainide after MI also demonstrated that mortality was significantly higher in patients receiving class I antiarrhythmic drugs (odds ratio = 1.14), than in patients not receiving an antiarrhythmic drug (113). None of the 59 studies showed a decrease in mortality by antiarrhythmic drugs (113).

Amiodarone is the antiarrhythmic drug with the highest success rate in maintenance of sinus rhythm after cardioversion of AF (109). However, in the Cardiac Arrest in Seattle: Conventional Versus Amiodarone Drug Evaluation Study, the incidence of pulmonary toxicity was 10% at two years in patients receiving amiodarone in a mean dose of 158 mg daily (114). The incidence of adverse effects from amiodarone also approaches 90% after five years of therapy (115).
Ventricular Rate Control

Because Maintenance of sinus rhythm with antiarrhythmic drugs may require serial cardioversions, it exposes patients to the risks of proarrrhythmia, sudden cardiac death, and other adverse effects, and requires the use of anticoagulants in patients in sinus rhythm who have a high risk of recurrence of AF, many cardiologists prefer the management strategy of ventricular rate control plus use of anticoagulants in patients with AF, especially in elderly patients with AF. β Blockers such as propranolol 10 mg to 30 mg given three to four times daily can be administered to control ventricular arrhythmias (116), and after conversion of AF to sinus rhythm. Should AF recur, β blockers have the added advantage of slowing down the ventricular rate. β Blockers are also the most effective drugs in preventing and treating AF after CABS (117).

The Pharmacological Intervention in the Atrial Fibrillation trial was a randomized trial of 252 patients with AF of between 7 and 360 days’ duration, which compared ventricular rate control (125 patients) with rhythm control (127 patients) (118). Diltiazem was used as first-line therapy in patients randomized to ventricular rate control. Amiodarone was used as first-line therapy in patients randomized to rhythm control. Amiodarone administration resulted in conversion of 23% of patients to sinus rhythm (118). Symptomatic improvement was reported in a similar percentage of patients in both groups. Assessment of quality of life showed no significant difference between the two treatment groups. The incidence of hospital admission was significantly higher in patients treated with rhythm control (69%) than in patients treated with ventricular rate control (24%) (118). Adverse drug effects caused a change in drug therapy in significantly more patients treated with rhythm control (25%) than in patients treated with ventricular rate control (14%) (118).

The Atrial Fibrillation Follow-Up Investigation of Rhythm Management (AFFIRM) study randomized 4060 patients, mean age 70 years (39% women), with paroxysmal or chronic AF of less than six months duration at high risk for stroke to either maintenance of AF with ventricular rate control, or to an attempt to maintain sinus rhythm with antiarrhythmic drugs after cardioversion (119). Patients in both arms of this study were treated with warfarin. All-cause mortality at five years was insignificantly increased by 15% in the maintenance of the sinus rhythm group compared with the ventricular rate control group (24% vs. 21 %, p = 0.08) (119). TE stroke was insignificantly reduced in the ventricular rate control group (5.5% vs. 7.1%), and all-cause hospitalization was significantly reduced in the ventricular rate control group (73% vs. 80%, p < 0.001) (119). In both groups, the majority of strokes occurred after warfarin was stopped, or when the INR was subtherapeutic. There was no significant difference in quality of life or functional status between the two treatment groups (119).

The Rate Control Versus Electrical Cardioversion for Persistent Atrial Fibrillation Study Group randomized 522 patients with persistent AF after a previous electrical cardioversion to receive treatment aimed at ventricular rate control or rhythm control (120). Both groups were treated with oral anticoagulants. At 2.3-year follow-up, the composite end point of death from cardiovascular causes, heart failure, TE complications, bleeding, implantation of a pacemaker, and severe adverse effects of drugs was 17.2% in the ventricular rate control group versus 22.6% in the rhythm control group (120). In this study, women randomized to rhythm control had a 3.1 times significant increase in cardiovascular morbidity or mortality, than women randomized to ventricular rate control (p = 0.002) (121).

The two-year mortality was similar in 1009 patients with AF and CHF treated with rate control or rhythm control (122). During 19-month follow-up of 110 patients with a
history of AF treated with antiarrhythmic drug therapy, recurrent AF was diagnosed by ECG recordings in 46% of the patients and by an implantable monitoring device in 88% of the patients (123). AF lasting longer than 48 hours was detected by the monitoring device in 50 of the 110 patients (46%) (123). Nineteen of these 50 patients (38%) were completely asymptomatic (123).

### Risk Factors for TE Stroke

Table 2 lists risk factors for TE stroke in patients with AF (1,2,24,25,124–135). In the SPAF Study involving patients, mean age 67 years, recent CHF (within three months), a history of hypertension, previous thromboembolism, echocardiographic left atrial enlargement, and echocardiographic LV systolic dysfunction were associated independently with the development of new TE events (129,132). The incidence of new TE events was 18.6% per year if three or more risk factors were present, 6.0% per year if one or two risk factors were present, and 1.0% per year if none of these risk factors was present (129).

In the SPAF Study III involving patients, mean age 72 years, patients were considered at high risk for developing TE stroke if they had either CHF or abnormal LV systolic function, prior thromboembolism, a systolic blood pressure of greater than 160 mmHg, or the patient was a woman older than age 75 years (130). In a study of 312 patients with chronic AF, mean age 84 years, independent risk factors for the development of new TE stroke were prior stroke (risk ratio = 1.6), rheumatic mitral stenosis (risk ratio = 2.0), LVH (risk ratio = 2.8), abnormal LVEF (risk ratio = 1.8), serum total cholesterol (risk ratio = 1.01 per 1 mg/dL increase), serum high-density lipoprotein cholesterol (risk ratio = 1.04 per 1 mg/dL decrease), and age (risk ratio = 1.03 per one year increase) (127).

### Antithrombotic Therapy

Prospective, randomized trials (125,126,130,133,136–142) and prospective, nonrandomized observational data from patients, mean age 83 years (131), and mean age 84 years (143), respectively, have documented that warfarin is effective in decreasing the

### Table 2  Risk Factors for Stroke in Patients with Atrial Fibrillation

<table>
<thead>
<tr>
<th>Risk Factor</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (1, 24, 124–128)</td>
</tr>
<tr>
<td>Echocardiographic left ventricular dysfunction (127–130)</td>
</tr>
<tr>
<td>History of heart failure (126, 130, 132)</td>
</tr>
<tr>
<td>Hypertension (125, 128, 130, 132)</td>
</tr>
<tr>
<td>Prior thromboembolic events (2, 24, 125–127, 129–133)</td>
</tr>
<tr>
<td>Women older than 75 years of age (130)</td>
</tr>
<tr>
<td>Rheumatic mitral stenosis (127, 128)</td>
</tr>
<tr>
<td>Mitral annular calcium (125, 134)</td>
</tr>
<tr>
<td>Diabetes mellitus (126)</td>
</tr>
<tr>
<td>History of myocardial infarction (125, 126, 128, 135)</td>
</tr>
<tr>
<td>Echocardiographic left atrial enlargement (128, 129)</td>
</tr>
<tr>
<td>Echocardiographic LVH (24, 25, 127, 128)</td>
</tr>
<tr>
<td>Extracranial carotid arterial disease (25)</td>
</tr>
<tr>
<td>Hypercholesterolemia (127)</td>
</tr>
<tr>
<td>Low serum high-density lipoprotein cholesterol (127)</td>
</tr>
</tbody>
</table>

References are shown in parenthesis.
incidence of TE stroke in patients with nonvalvular AF. Analysis of pooled data from five randomized, placebo-controlled studies showed that warfarin significantly decreased the incidence of new TE stroke by 68%, and was significantly more effective than aspirin in decreasing the incidence of new TE stroke (126). In the Veterans Affairs Cooperative study, the incidence of new TE events was 4.3% per year in patients on placebo versus 0.9% per year in patients on warfarin in patients with no prior stroke, 9.3% per year in patients on placebo versus 6.1% per year in patients on warfarin in patients with prior stroke, and 4.8% per year in patients on placebo versus 0.9% per year in patients on warfarin in patients older than age 70 years (140). In the European Atrial Fibrillation Trial involving patients with recent transient cerebral ischemic attack or minor ischemic stroke, at 2.3-year follow-up, the incidence of new TE events was 12% per year in patients taking placebo, 10% per year in patients taking aspirin, and 4.0% per year in patients taking warfarin (133).

Nonrandomized observational data from older patients with chronic AF, mean age 83 years, found that 141 patients treated with oral warfarin to achieve an INR between 2.0 and 3.0 (mean INR was 2.4) had a 67% significant decrease in new TE stroke, compared with 209 patients treated with oral aspirin (131). Compared with aspirin, warfarin caused a 40% significant decrease in new TE stroke in patients with prior stroke, a 31% significant decrease in new TE stroke in patients with no prior stroke, a 45% significant reduction in new TE stroke in patients with abnormal LVEF, and a 36% significant reduction in new TE stroke in patients with normal LVEF (131).

At 1.1-year follow-up in the SPAF Study III, patients with AF considered to be at high risk for developing new TE stroke—who were randomized to treatment with oral warfarin to achieve an INR between 2.0 and 3.0 (mean INR was 2.4) had a 72% significant decrease in ischemic stroke or systemic embolism, compared with patients randomized to treatment with oral aspirin 325 mg daily plus oral warfarin to achieve an INR between 1.2 and 1.5 (130). Adjusted-dose warfarin caused an absolute decrease in ischemic stroke or systemic embolism of 6.0% per year (130). In the second Copenhagen Atrial Fibrillation, Aspirin, Anticoagulation (AFASK) study, low-dose warfarin plus aspirin was also less effective in reducing stroke or systemic TE events in patients with AF (7.2% after one year), than was adjusted-dose warfarin to achieve an INR between 2 and 3 (2.8% after one year) (142).

Analysis of pooled data from five randomized controlled studies demonstrated that the annual incidence of major hemorrhage was 1.0% for the control group, 1.0% for the aspirin group, and 1.3% for the warfarin group (126). The incidence of major hemorrhage in patients, mean age 72 years, taking adjusted-dose warfarin to achieve an INR of 2 to 3 in the SPAF III study was 2.1% (130). In the second Copenhagen AFASK study, the incidence of major hemorrhage in patients, mean age 73 years, was 0.8% per year for patients treated with adjusted-dose warfarin to achieve an INR between 2 and 3 and 1.0% per year for patients treated with aspirin 300 mg daily (142). The incidence of major hemorrhage in older patients with chronic AF, mean age 83 years, was 4.3% (1.4% per year) in patients treated with warfarin to maintain an INR between 2.0 and 3.0, and 2.9% (1.0% per year) in patients treated with aspirin 325 mg daily (131).

In the SPAF III Study, 892 patients, mean age 67 years, at low risk for developing TE stroke were treated with oral aspirin 325 mg daily (144). The incidence of ischemic stroke or systemic embolism was 2.2% per year (144). The incidence of ischemic stroke or systemic embolism was 3.6% per year in patients with a history of hypertension and 1.1% per year in patients with no history of hypertension (144).

In a study of 13,559 patients with nonvalvular AF hospitalized with an outpatient stroke, compared with an INR of 2.0 or greater, an INR of less than 2.0 at hospital admission significantly increased the odds of a severe stroke by 1.9 times and the risk of
death within 30 days by 3.4 times (145). The 30-day mortality was similar among patients who were taking aspirin or warfarin with an INR of less than 2.0 (145). Elderly patients taking warfarin should have an INR maintained between 2 and 3, not one less than 2.0 or more than 3.5 (146).

On the basis of the available data, patients with chronic or paroxysmal AF at high risk for developing TE stroke or with a history of hypertension and who have no contraindications to anticoagulation therapy should be treated with long-term oral warfarin to achieve an INR between 2 and 3 (98,147). Hypertension must be controlled. Whenever the patient has a prothrombin time taken, the blood pressure should also be checked. The physician prescribing warfarin should be aware of the numerous drugs which potentiate the effect of warfarin causing an increased prothrombin time and risk of bleeding (148). Patients with AF at low risk for developing TE stroke or with contraindications to treatment with long-term oral warfarin should be treated with aspirin 325 mg taken orally, daily (149).

Patients younger than age 60 years in Olmstead County, Minnesota, with lone AF (no heart disease) had a low risk of TE stroke at 15-year follow-up (150). However, at 30-year follow-up in the Framingham Heart Study, the age-adjusted percentage of patients with lone AF who developed a cerebrovascular event was 28% versus 7% in the control group (151). Table 3 shows the ACC/AHA/ESC Class I indications for antithrombotic therapy in the management of patients with AF (147).

Despite the data showing the efficacy of oral warfarin used in a dose to achieve an INR between 2.0 and 3.0 in reducing the incidence of new TE events in patients with paroxysmal or chronic AF, only about one-third of patients with AF who should be taking warfarin receive it (152). In an academic hospital-based geriatrics practice, only 61 of 124 patients (49%), mean age 80 years, with chronic AF at high risk for developing TE stroke and no contraindications to warfarin were being treated with warfarin therapy (5).

Elderly patients have a higher prevalence and incidence of AF than younger patients (1–6). Elderly patients with AF are at higher risk for developing TE stroke than are younger patients with AF (1,22,24,124–128). However, physicians are more reluctant to treat elderly patients with AF with warfarin therapy. Hopefully, intensive physician education will help solve this important clinical problem.

In the Anticoagulation and Risk Factor in Atrial Fibrillation Study, women off warfarin had significantly higher annual rates of thromboembolism (3.5%) than men

### Table 3  ACC/AHA/ESC Class I Indications for Treating Patients With Atrial Fibrillation with Antithrombotic Therapy

<table>
<thead>
<tr>
<th>Therapy</th>
<th>Class I Indications</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aspirin</td>
<td>Aspirin 81 to 325 mg daily for patients with no risk factors</td>
</tr>
<tr>
<td></td>
<td>Aspirin 81 to 325 mg daily or warfarin to maintain an INR between 2.0–3.0 for patients with 1 moderate-risk factor</td>
</tr>
<tr>
<td>Warfarin</td>
<td>Warfarin to maintain an INR between 2.0–3.0 for patients with any high-risk factor or more than 1 moderate-risk factor</td>
</tr>
</tbody>
</table>

*Note*: Moderate-risk factors include age ≥75 years, hypertension, heart failure, LVEF ≤35%, or diabetes mellitus. High-risk factors include prior stroke, transient ischemic attack or embolism, mitral stenosis, prosthetic heart value.

*If mechanical valve, the INR should be maintained between 2.5–3.5.*

**Abbreviations**: ACC/AHA/ESC, American College of Cardiology/American Heart Association/European Society for Cardiology; INR, international normalized ratio.

**Source**: From Ref. 147.
(1.8%) (153). Warfarin was associated with significantly lower adjusted TE rates for both women (60% reduction) and men (40% reduction) with similar annual rates of major bleeding (1.0% and 1.1%, respectively) (153).

The Atrial Fibrillation Clopidogrel Trial with Irbesartan for the Prevention of Vascular Events (ACTIVE W) demonstrated in patients with AF that the annual risk of first occurrence of stroke, non–central nervous system systemic embolus, MI, or vascular death was 3.93% in 3371 patients randomized to warfarin to maintain an INR between 2.0 and 3.0, and 5.60% in 3335 patients randomized to clopidogrel 75 mg daily plus aspirin 75 to 100 mg daily, with a 44% significant reduction in the primary outcome attributed to warfarin (154). The incidence of major bleeding was 10%, insignificantly higher in patients treated with clopidogrel plus aspirin than in persons treated with warfarin (154).

**ATRIAL FLUTTER**

Atrial flutter (AFL) may be paroxysmal or chronic. Episodes of AFL and of AF may occur in the same patient. The AFL waves are usually best seen in leads II, III, aVF, and V1. The atrial rate usually ranges from 250 to 350 beats per minute and is most commonly 300 beats per minute. There is no isoelectric interval between the AFL waves. In the absence of drug therapy, there is usually a 2:1 AV conduction response.

In the general population, the incidence of AFL increases with age and ranges from 5 per 100,000 persons younger than 50 years to 587 per 100,000 persons older than 80 years (155). At highest risk of developing AFL are the elderly, men, and patients with CHF or chronic obstructive lung disease (155). Documented structural heart disease or a predisposing condition such as a major surgical procedure or pneumonia was present in 178 of 181 patients (98%) with AFL (155).

The acute onset of AFL with a rapid ventricular rate reduces cardiac output and may lead to angina pectoris, CHF, hypotension, acute pulmonary edema, and syncope. Chronic AFL with a rapid ventricular rate can cause a tachycardia-mediated cardiomyopathy. Patients with AFL are also at increased risk for developing new TE stroke (156,157). Left atrial appendage stunning occurs after cardioversion in patients with AFL, although to a lesser degree than in patients with AF (158).

**Management**

Management of AFL is similar to management of AF. DC cardioversion is the treatment of choice for converting AFL to sinus rhythm (159). Thirty-eight percent of 78 patients with AFL treated with intravenous ibutilide, converted to sinus rhythm (95). Fifty-four percent of 16 patients with AFL treated with intravenous dofetilide converted to sinus rhythm (93). Atrial pacing may also be used to try to convert AFL to sinus rhythm (160).

Intravenous verapamil (40), diltiazem (39), or β blockers (35–38) may be used to immediately slow a very rapid ventricular rate associated with AFL. Oral verapamil (46), diltiazem (45), or β blockers (47) should be added to the therapeutic regimen if a rapid ventricular rate associated with AFL occurs at rest or during exercise, despite digoxin. Amiodarone is the most effective drug for slowing a rapid ventricular rate associated with AFL (49). Digoxin, verapamil, and diltiazem are contraindicated in patients with AFL associated with the WPW syndrome because these drugs shorten the refractory period of the accessory AV pathway, causing more rapid conduction down the accessory pathway. Class I antiarrhythmic drugs such as quinidine should never be used to treat patients with AFL who are not being treated with digoxin, a β blocker, verapamil, or diltiazem as
Supraventricular Tachyarrhythmias in the Elderly

a 1:1 AV conduction response may develop. Drugs used to treat AFL may also be proarrhythmic (89,90).

Since patients with AFL are at increased risk for developing new TE stroke (156,157), anticoagulant therapy should be administered prior to DC cardioversion, or drug cardioversion of patients of AFL to sinus rhythm using the same guidelines as for converting AF (98–102). Patients with chronic AFL should be treated with oral warfarin with the INR maintained between 2.0 and 3.0 (98).

Radiofrequency catheter ablation of AFL is a highly successful procedure, especially when the right atrial isthmus is incorporated in the AFL circuit (161,162). Demonstration of bidirectional isthmus block after catheter ablation predicts a high long-term success rate (162). A second radiofrequency catheter ablation may be needed in up to one-third of patients, especially in those with right atrial enlargement (161). Radiofrequency catheter ablation was successful in converting 63 of 70 patients (90%), mean age 78 ± 5 years, with AFL to sinus rhythm (59).

PAROXYSMAL SUPRAVENTRICULAR TACHYCARDIA

Paroxysmal supraventricular tachycardia (PSVT) is a regular, narrow, and complex tachycardia with a rate usually between 140 and 220 beats per minute. A wide QRS complex occurs in the presence of bundle branch block or aberrant ventricular conduction. If aberrant ventricular conduction is present, the QRS complex is usually less than 140 milliseconds, and a right bundle branch block pattern is present 85% of the time.

PSVT is usually caused by reentry, but may be caused by abnormal automaticity or by triggered activity. AV nodal reentrant tachycardia (AVNRT) accounts for 60% of episodes of PSVT (163). Discrete P waves are not seen on the 12-lead ECG in two-thirds of these patients. Retrograde P waves (inverted in leads II, III, and aVF) following the QRS complex occur in approximately 30% of these patients. In approximately 10% of patients, the reentry circuit is reversed with anterograde conduction over the fast pathway and retrograde conduction over the slow pathway (163). This type of PSVT is referred to as uncommon AVNRT, and the RP interval is longer than the PR interval.

PSVT secondary to accessory pathway conduction occurs in 30% of patients with sustained PSVT (164). Accessory pathway conduction can be overt as in the WPW syndrome or concealed, because accessory pathways are capable of either unidirectional or bidirectional conduction.

Paroxysmal atrial tachycardia includes those forms of PSVT that do not involve the AV node as an obligate part of the tachycardia circuit (165). Atrial tachycardias can be reentrant, automatic, or triggered in origin (165).

The prevalence of short bursts of PSVT diagnosed by 24-hour AECGs in 1476 elderly persons, mean age 81 years, with heart disease was 33% (22). At 42-month follow-up of 1359 persons, mean age 81 years, with heart disease, short bursts of PSVT were not associated with an increased incidence of new coronary events (17). At 43-month follow-up of 1476 persons, mean age 81 years, with heart disease, short bursts of PSVT were not associated with an increased incidence of new TE stroke (22).

Management

Sustained episodes of supraventricular tachycardia (SVT) should first be treated by increasing vagal tone by carotid sinus massage, the Valsalva maneuver, facial immersion in cold water, or administration of phenylephrine (166). If vagal maneuvers are unsuccessful,
Intravenous adenosine is the drug of choice (167). Intravenous verapamil, diltiazem, or β blockers may also be used. If these measures do not convert PSVT to sinus rhythm, DC cardioversion should be used.

Most patients with PSVT do not require long-term therapy. If long-term treatment is required because of symptoms due to frequent episodes of PSVT, then digoxin, propranolol, verapamil, or diltiazem may be administered (168). These drugs are the initial drug of choice for AVNRT and AV reentrant SVT. For PSVT associated with the WPW syndrome, flecainide or propafenone may be used if there is no associated heart disease (169). If heart disease is present, quinidine, procainamide, or disopyramide plus a β blocker or verapamil should be used (169). Radiofrequency catheter ablation should be used to treat older persons with symptomatic, drug-resistant SVT and should be considered an early treatment option (170). Radiofrequency catheter ablation can be successfully performed in older patients with low complication rates. Resultant complete heart block for slow pathway ablation in AVNRT occurs in patients exhibiting a significantly prolonged baseline first-degree AV block. Cardiac perforation risk is also increased in elderly women. Radiofrequency catheter ablation was successful in converting 60 of 66 patients, mean age 78 ± 5 years, with SVT to sinus rhythm (59).

**Accelerated Atrioventricular Junctional Rhythm**

Accelerated AV junctional rhythm also called nonparoxysmal AV junctional tachycardia (NPJT) is a form of SVT caused by enhanced impulse formation within the AV junction, rather than by reentry (171). This arrhythmia is usually due to recent aortic or mitral valve surgery, acute MI, or digitalis toxicity. The ventricular rate usually ranges between 70 and 130 beats per minute. Treatment of NPJT is directed toward correction of the underlying disorder. Hypokalemia, if present, should be treated with potassium. Digitalis should be stopped if digitalis toxicity is present. β Blockers may be given cautiously if this is warranted by clinical circumstances.

**Paroxysmal Atrial Tachycardia with Atrioventricular Block**

Digitalis toxicity causes 70% of cases of paroxysmal atrial tachycardia (PAT) with AV block. Digoxin and diuretics causing hypokalemia should be stopped in these persons. If the serum potassium is low or low-normal, potassium chloride is the treatment of choice. Intravenous propranolol will cause conversion to sinus rhythm in about 85% of patients with digitalis-induced PAT with AV block and in about 35% of patients with PAT with AV block not induced by digitalis (166). By increasing AV block, propranolol may also be beneficial in slowing a rapid ventricular rate in PAT with AV block (166).

**Multifocal Atrial Tachycardia**

Multifocal atrial tachycardia (MAT) is usually associated with acute illness, especially in older persons with pulmonary disease. MAT is best managed by treatment of the underlying disorder. Intravenous verapamil has been reported to be effective in controlling the ventricular rate in MAT, with occasional conversion to sinus rhythm (172). However, one of the authors found intravenous verapamil not very effective in treating MAT (173). The tendency of intravenous verapamil to aggravate preexisting arterial hypoxemia also limits its use in the group of patients most likely to develop MAT (172).
REFERENCES


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Ventricular Arrhythmias in the Elderly

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The presence of three or more consecutive ventricular premature complexes (VPCs) on an electrocardiogram (ECG) is diagnosed as ventricular tachycardia (VT) (1,2). VT is considered sustained if it lasts for 30 seconds or more, and nonsustained if it lasts less than 30 seconds (2). Complex ventricular arrhythmias (VA) include VT or paired, multiform, or frequent VPC. This author considers frequent VPCs an average of more than or equal to 30/hr or more on a 24-hour ambulatory electrocardiogram (AECG), or more than or equal to 6/min or more on a one-minute rhythm strip of an ECG (2,3). Simple VA include infrequent VPCs and no complex forms.

PREVALENCE OF COMPLEX VENTRICULAR ARRHYTHMIAS

The prevalence of nonsustained VT detected by 24-hour AECGs was 4% in 98 older, disease-free persons in the Baltimore Longitudinal Study of Aging (1); 4% in 106 active older persons (4); 2% in 50 older persons without cardiovascular disease (5); 4% in 729 older women and 13% in 643 older men in the Cardiovascular Health Study (6); 3% in 135 older men and 2% in 297 older women without cardiovascular disease (7); 9% in 385 older men and 8% in 806 older women with hypertension, valvular disease, or cardiomyopathy (7); and 16% in 395 older men and 15% in 771 older women with coronary artery disease (CAD) (7). The prevalence of complex VA in older persons in these studies was 50% (1), 31% (4), and 20% (5), respectively; 16% in women and 28% in men (6); 31% in older men and 30% in older women without cardiovascular disease (7); 54% in older men and 55% in older women with hypertension, valvular disease, or cardiomyopathy (7); and 69% in older men and 68% in older women with CAD (7).

In 104 older persons, mean age 82 years, without cardiovascular disease who had a 12-lead ECG with a one-minute rhythm strip obtained within 24 hours of a 24-hour...
AECG, complex VA were present on the 24-hour AECGs in 33% of persons and on the one-minute rhythm strips in 2% of persons (3). In this study, in 843 older persons, mean age 82 years, with cardiovascular disease, complex VA were present on the 24-hour AECGs in 55% of persons and on the one-minute rhythm strips in 4% of persons (3).

In older persons with cardiovascular disease, those with an abnormal left ventricular ejection fraction (LVEF) (8), with echocardiographic LV hypertrophy (9), or with silent myocardial ischemia (10) have a higher prevalence of VT and of complex VA than those with normal LVEF, normal LV mass, and no myocardial ischemia.

**PROGNOSIS OF VENTRICULAR ARRHYTHMIAS**

**No Heart Disease**

In the Baltimore Longitudinal Study of Aging, nonsustained VT or complex VA were not associated with an increased incidence of new coronary events at 10-year follow-up in 98 older subjects with no clinical evidence of heart disease (11). In this study also, exercise-induced nonsustained VT was not associated with an increased incidence of new coronary events at two-year follow-up in older persons with no clinical evidence of heart disease (12). And at 5.6-year follow-up in this study, exercise-induced frequent or repetitive VPCs were not associated with an increased incidence of new coronary events in older persons with no clinical evidence of heart disease either (13).

Nonsustained VT or complex VA diagnosed by 24-hour AECGs were not associated with an increased incidence of new coronary events at two-year follow-up in 76 older persons with no clinical evidence of heart disease (14), and were not associated with an increased incidence of primary ventricular fibrillation (VF) or sudden cardiac death in 86 older persons with no clinical evidence of heart disease (15). Complex VA diagnosed by 24-hour AECGs or by 12-lead ECGs with one-minute rhythm strips were also not associated with an increased incidence of new coronary events at 39-month follow-up in 104 older persons with no clinical evidence of heart disease (3). Nonsustained VT or complex VA diagnosed by 24-hour AECGs were not associated with an increased incidence of new coronary events at 45-month follow-up of 135 men and at 47-month follow-up of 297 women without cardiovascular disease (7).

Because nonsustained VT or complex VA are not associated with an increased incidence of new coronary events in older persons with no clinical evidence of heart disease, asymptomatic nonsustained VT or complex VA in older persons without heart disease should not be treated with antiarrhythmic drugs. Because simple VA in older persons with heart disease are not associated with an increased incidence of new coronary events (3,7,11,14,15), simple VA in older persons without heart disease should not be treated with antiarrhythmic drugs.

**Heart Disease**

Numerous studies have documented that patients with VT or with complex VA associated with heart disease are at increased risk for developing new coronary events (16–19). Prospective studies in older persons, mean age 82 years, with heart disease also demonstrated that nonsustained VT and complex VA were significantly associated with an increased incidence of new coronary events, and with an increased incidence of primary VF or sudden cardiac death (Table 1) (3,7,11,14,15).
MEDICAL THERAPY

General Measures

Underlying causes of complex VA should be treated, if possible. Treatment of congestive heart failure (CHF), digitalis toxicity, hypokalemia, hypomagnesemia, hypertension, LV dysfunction, LV hypertrophy, myocardial ischemia by anti-ischemic drugs such as β blockers or by coronary revascularization, hypoxia, and other conditions may abolish or

Table 1  Association of Complex Ventricular Arrhythmias and Ventricular Tachycardia with New Coronary Events in Elderly Patients with Heart Disease

<table>
<thead>
<tr>
<th>Study (Ref.)</th>
<th>Mean age (yr)</th>
<th>Cardiac status</th>
<th>Follow-up (mo)</th>
<th>Incidence of new coronary events</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aronow et al. (n = 843) (3)</td>
<td>82</td>
<td>Heart disease</td>
<td>39</td>
<td>Increased 1.7 times by complex VA</td>
</tr>
<tr>
<td>Aronow et al. (n = 391) (14)</td>
<td>82</td>
<td>Heart disease</td>
<td>24</td>
<td>With normal LVEF, increased 2.5 times by complex VA and 3.2 times by VT; increased 7.6 times by complex VA plus abnormal LVEF and increased 6.8 times by VT plus abnormal LVEF</td>
</tr>
<tr>
<td>Aronow et al. (n = 468) (15)</td>
<td>82</td>
<td>Heart disease</td>
<td>27</td>
<td>With no LVH, SCD, or VF increased 2.4 times by complex VA and 1.8 times by VT; SCD, or VF increased 7.3 times by complex VA plus LVH and increased 7.1 times by VT plus LVH</td>
</tr>
<tr>
<td>Aronow et al. (n = 404) (10)</td>
<td>82</td>
<td>Heart disease</td>
<td>37</td>
<td>Increased 1.7 times by VT and 2.4 times by complex VA; increased 2.5 times by VT plus SI and 4.0 times by complex VA plus SI</td>
</tr>
<tr>
<td>Aronow et al. (n = 395 men) (7)</td>
<td>80</td>
<td>CAD</td>
<td>45</td>
<td>Increased 2.4 times by complex VA and 1.7 times by VT</td>
</tr>
<tr>
<td>Aronow et al. (n = 385 men) (7)</td>
<td>80</td>
<td>HT, VD, or CMP</td>
<td>45</td>
<td>Increased 1.9 times by complex VA and 1.9 times by VT</td>
</tr>
<tr>
<td>Aronow et al. (n = 771 women) (7)</td>
<td>81</td>
<td>CAD</td>
<td>47</td>
<td>Increased 2.5 times by complex VA and 1.7 times by VT</td>
</tr>
<tr>
<td>Aronow et al. (n = 806 women) (7)</td>
<td>81</td>
<td>HT, VD, or CMP</td>
<td>47</td>
<td>Increased 2.2 times by complex VA and 2.0 times by VT</td>
</tr>
</tbody>
</table>

Abbreviations: VA, ventricular arrhythmias; VT, ventricular tachycardia; LVEF, left ventricular ejection fraction; LVH, left ventricular hypertrophy; SCD, sudden coronary death; VF, primary ventricular fibrillation; CAD, coronary artery disease; HT, hypertension; VD, valvular heart disease; CMP, cardiomyopathy; SI, silent ischemia.
reduce complex VA. The older person should not smoke or drink alcohol and should avoid drugs that may cause or increase complex VA.

All older persons with CAD should be treated with aspirin (20–23), with β blockers (23–28), with angiotensin-converting enzyme (ACE) inhibitors (23,28–33), and with 3'-hydroxy-3'-methylglutaryl coenzyme A reductase inhibitors (23,34–40) unless there are contraindications to these drugs. The serum low-density lipoprotein (LDL) cholesterol level should be reduced to less than 70 mg/dL (40). The serum LDL cholesterol level should be reduced at least 30% to 40% (40).

Age-related physiologic changes may affect absorption, distribution, metabolism, and excretion of cardiovascular drugs (41). There are numerous physiologic changes with aging that affect pharmacodynamics with alterations in end-organ responsiveness to cardiovascular drugs (41). Drug interactions between antiarrhythmic drugs and other cardiovascular drugs are common, especially in older persons (41). There are also important drug-disease interactions that occur in older persons (41). Class I antiarrhythmic drugs have an unacceptable proarrhythmia rate in patients with heart disease and should be avoided. Class III antiarrhythmic drugs should also be used with caution in older patients with heart disease since multiple factors may increase the incidence of proarrhythmia. Except for β blockers, all antiarrhythmic drugs may cause torsades de pointes (VT with polymorphous appearance associated with prolonged QT interval).

Class I Antiarrhythmic Drugs

Class I antiarrhythmic drugs are sodium channel blockers. Class Ia antiarrhythmic drugs have intermediate channel kinetics and prolong repolarization. These drugs include quinidine, procainamide, and disopyramide. Class Ib antiarrhythmic drugs have rapid channel kinetics and slightly shorten repolarization. These drugs include lidocaine, mexilitine, tocainide, and phenytoin. Class Ic drugs have slow channel kinetics and have little effect on repolarization. These drugs include encainide, flecainide, moricizine, propafenone, and lorcainide. None of the class I antiarrhythmic drugs have been demonstrated in controlled, clinical trials to reduce sudden cardiac death, total cardiac death, or total mortality.

The International Mexilitine and Placebo Antiarrhythmic Coronary Trial (IMPACT) was a prospective, double-blind, randomized study in survivors of myocardial infarction (MI), mean age 57 years, in whom 317 persons were randomized to mexilitine and 313 persons to placebo (42). Complex VA were present on 24-hour AECGs at study entry in 31% of persons randomized to mexilitine and in 38% of persons randomized to placebo. At one-year follow-up, mortality was 7.6% for mexilitine-treated patients versus 4.8% for placebo-treated patients (42).

The Cardiac Arrhythmia Suppression Trial (CAST) I was a prospective, double-blind, randomized study in survivors of MI with asymptomatic or mildly symptomatic VA in which 730 patients were randomized to encainide or flecainide and 725 patients to placebo (43). The prevalence of nonsustained VT was 21%. Mean LVEF was 40%. Thirty-eight percent of patients were 66 to 79 years of age. Adequate suppression of VA by encainide or flecainide was required before randomization. Despite adequate suppression of VA, at 10-month follow-up, encainide and flecainide significantly increased mortality from arrhythmia or cardiac arrest [relative risk = 3.6; 95% confidence interval (CI), 1.7–8.5] and significantly increased total mortality (relative risk = 2.5; 95% CI, 1.6–4.5) (41). Older age increased the likelihood of adverse events, including death, in patients receiving encainide and flecainide (44).

CAST II was a prospective, double-blind, randomized study in survivors of MI with asymptomatic or mildly symptomatic VA in which 581 patients were randomized to moricizine and 574 patients to placebo (45). The prevalence of nonsustained VT was
Ventricular Arrhythmias in the Elderly

30%. Mean LVEF was 33%. Thirty-eight percent of patients were 66 to 79 years old. Adequate suppression of VA by moricizine was required before randomization. At 18-month follow-up, the mortality from arrhythmia or cardiac arrest was 8.4% for patients treated with moricizine and 7.3% for patients treated with placebo (45). The two-year survival rate was 81.7% for patients treated with moricizine and 85.6% for patients treated with placebo (45). The investigators concluded that the use of moricizine in this study was “…not only ineffective but also harmful” (45). Older age increased the likelihood of adverse events, including death, in patients receiving moricizine (44).

An analysis of the CAST I and II studies showed that older age was an independent predictor of adverse events (relative risk 1.30 per decade of age) (44). On the basis of the CAST I and CAST II data, the author would not use encainide, flecainide, or moricizine for the treatment of VT or complex VA in older or younger patients with heart disease.

Aronow et al. (46) performed a prospective study in 406 older persons, mean age 82 years, with heart disease (58% with prior MI) and asymptomatic complex VA diagnosed by 24-hour AECGs. The prevalence of nonsustained VT was 20%. The incidence of adverse effects causing cessation of drug was 48% for quinidine and 55% for procainamide. Of 406 older persons, 220 were treated with quinidine (n = 213) or procainamide (n = 7) and 186 with no antiarrhythmic drug. Follow-up 24-hour AECGs in 25 persons with nonsustained VT, and in 104 persons with complex VA showed that quinidine or procainamide decreased nonsustained VT more than 90% in 84% of the persons, and decreased the average number of VPCs/hr more than 70% in 84% of the persons (46).

At 24-month follow-up, the incidences of sudden cardiac death, total cardiac death, and of total death were not significantly different in persons treated with quinidine or procainamide or with no antiarrhythmic drug (46). The incidence of total mortality was 65% for persons treated with quinidine or procainamide and 63% for persons treated with no antiarrhythmic drug. Quinidine or procainamide did not decrease sudden cardiac death, total cardiac death, or total death in comparison with no antiarrhythmic drug in older patients with ischemic or nonischemic heart disease, abnormal or normal LV ejection fraction, and presence versus absence of VT (46).

Moosvi et al. (47) performed a retrospective analysis of the effect of empiric antiarrhythmic therapy in 209 resuscitated out-of-hospital cardiac arrest patients, mean age 62 years, with CAD. Of the 209 patients, 48 received quinidine, 45 received procainamide, and 116 received no antiarrhythmic drug. The two-year sudden death survival was 69% for quinidine-treated patients, 69% for procainamide-treated patients, and 89% for patients treated with no antiarrhythmic drug (p < 0.01) (47). The two-year total survival was 61% for quinidine-treated patients, 57% for procainamide-treated patients, and 71% for patients treated with no antiarrhythmic drug (p < 0.05) (47).

Hallstrom et al. (48) performed a retrospective analysis of the effect of antiarrhythmic drug use in 941 patients, mean age 62 years, resuscitated from prehospital cardiac arrest attributable to VF between 1970 and 1985. Quinidine was administered to 19% of the patients, procainamide to 18% of the patients, β blockers to 28% of the patients, and no antiarrhythmic drug to 39% of the patients. There was an increased incidence of death or recurrent cardiac arrest in patients treated with quinidine or procainamide versus no antiarrhythmic drug (adjusted relative risk = 1.17; 95% CI, 0.98–1.41). Survival was significantly worse for patients treated with procainamide than for patients treated with quinidine (adjusted relative risk = 1.57; 95% CI, 1.21–2.07) (48).

A meta-analysis of six double-blind studies comprising 808 patients with chronic atrial fibrillation who underwent direct-current cardioversion to sinus rhythm showed that the mortality at one year was significantly higher in patients treated with quinidine
(2.9%), than in patients treated with placebo (0.8%) \( (p < 0.05) \) (49). Of 1330 patients in the Stroke Prevention in Atrial Fibrillation Study, 127 were receiving quinidine, 57 procainamide, 15 disopyramide, 34 flecainide, 20 encainide, and 7 amiodarone (50). The adjusted relative risk of cardiac mortality was 1.8 times higher (95% CI, 0.7–3.7) and the adjusted relative risk of arrhythmic death was 2.1 times higher (95% CI, 0.8–5.0) in patients on antiarrhythmic drugs, than in patients not on antiarrhythmic drugs (50). In patients with a history of CHF, the adjusted relative risk of cardiac death was 3.3 times higher (95% CI, 1.1–8.2) and the adjusted relative risk of arrhythmic death was 5.8 times higher (95% CI, 1.2–13.5) in patients receiving antiarrhythmic drugs, than in patients not receiving antiarrhythmic drugs (50).

Morganroth and Goin (51) performed a meta-analysis of four randomized, double-blind, controlled trials lasting 2 to 12 weeks in which quinidine \( (n = 502) \) was compared with flecainide \( (n = 141) \), mexiletine \( (n = 246) \), tocainide \( (n = 67) \), and propafenone \( (n = 53) \) in the treatment of complex VA. There was an increased risk of mortality in patients treated with quinidine compared with patients treated with the other antiarrhythmic drugs (absolute risk increase \( = 1.6\%; 95\% \text{ CI}, 0–3.1\%) \) (51).

Teo et al. (52) analyzed 59 randomized controlled trials comprising 23,229 patients that investigated the use of class I antiarrhythmic drugs after MI. The class I drugs investigated included quinidine, procainamide, disopyramide, imipramine, moricizine, lidocaine, tocinamide, phenytoin, mexiletine, aprindine, encaimide, and flecainide. Mortality was significantly higher in patients receiving class I antiarrhythmic drugs than in patients receiving no antiarrhythmic drugs (odds ratio \( = 1.14; 95\% \text{ CI}, 1.01–1.28\)). None of the 59 studies demonstrated that the use of a class I antiarrhythmic drug decreased mortality in postinfarction patients (52).

On the basis of the data from the studies discussed in this section, none of the class I antiarrhythmic drugs should be used for the treatment of VT or complex VA in older or younger patients with heart disease.

**Calcium Channel Blockers**

Calcium channel blockers are not useful in the treatment of complex VA. Although verapamil can terminate a left septal fascicular VT, hemodynamic collapse can occur if intravenous verapamil is administered to patients with the more common forms of reentry VT. Teo et al. (52) analyzed randomized, controlled trials comprising 20,342 patients that investigated the use of calcium channel blockers after MI. Mortality was insignificantly higher in patients receiving calcium channel blockers than in patients receiving no antiarrhythmic drugs (odds ratio \( = 1.04; 95\% \text{ CI}, 0.95–1.14\)) (52). On the basis of these data, none of the calcium channel blockers should be used in the treatment of VT or complex VA in older or younger patients with heart disease.

**β Blockers**

Teo et al. (52) analyzed 55 randomized, controlled trials comprising 53,268 patients that investigated the use of β blockers after MI. Mortality was significantly reduced in patients receiving β blockers compared with control patients (odds ratio \( = 0.81; 95\% \text{ CI}, 0.75–0.87\)) (52).

β Blockers caused a greater reduction in mortality in older persons after MI, than in younger persons after MI (24–27,53). The decrease in mortality after MI in persons treated with β blockers was due to both a reduction in sudden cardiac death and recurrent MI (24–27,53).

The Beta Blocker Heart Attack Trial was a double-blind, randomized study which included 3290 patients after MI (53–55). Thirty-three percent of the patients were 60 to
69 years of age. At 25-month follow-up, propranolol decreased sudden cardiac death by 28% in patients with complex VA, and by 16% in patients without complex VA. Propranolol significantly reduced total mortality by 34% in patients aged 60–69 yr (p = 0.01) and insignificantly reduced total mortality by 19% in patients aged 30 to 59 years (Table 2) (53–55).

β Blockers reduce complex VA including VT (55–57). β Blockers also increase VF threshold in animal models and have been found to decrease VF in patients with acute MI (58). A randomized, double-blind, placebo-controlled study of propranolol in high-risk survivors of acute myocardial infarction treated with propranolol for 1 yr had a 52% significant reduction in sudden cardiac death (58).

β Blockers reduce myocardial oxygen demand and decrease myocardial ischemia, which may reduce the likelihood of VF. Stone et al. (59) showed by 48-hour AECGs in 50 patients with stable angina pectoris that propranolol, but not diltiazem or nifedipine, caused a significant reduction in the mean number of episodes of myocardial ischemia, and in the mean duration of myocardial ischemia compared with placebo. β Blockers also decrease sympathetic tone, increase vagal tone, and stabilize cardiac membrane potentials, which reduces the likelihood of VF. In addition, β blockers are antithrombotic (60) and may prevent atherosclerotic plaque rupture (61).

In the retrospective study by Hallstrom et al. (48) in 941 patients, mean age 62 years, resuscitated from prehospital cardiac arrest attributed to VF, β blockers were administered to 28% of the patients and no antiarrhythmic drug to 39% of the patients. At 108-month follow-up, patients treated with β blockers had a significant decreased incidence of death.
or recurrent cardiac arrest compared with patients treated with no antiarrhythmic drug (adjusted relative risk = 0.62; 95% CI, 0.50–0.77) (Table 2) (48).

Aronow et al. (62) performed a prospective study in 245 older persons, mean age 81 years, with heart disease (64% with prior MI and 36% with hypertensive heart disease), complex VA and no sustained VT diagnosed by 24-hour AECGs, and an LVEF of 40% or more. Nonsustained VT occurred in 32% of patients. Silent myocardial ischemia occurred in 33% of patients. Of the 245 patients, 123 were randomized to propranolol and 122 to no antiarrhythmic drug. Follow-up was for 29 months. Propranolol was discontinued because of adverse effects in 14 of 123 patients (11%).

Follow-up 24-hour AECGs were obtained at a median of six months in 91% of patients treated with propranolol and in 89% of patients treated with no antiarrhythmic drug (62). Propranolol was significantly more effective than no antiarrhythmic drug in reducing VT by more than 90% (71% vs. 25% of patients) \( (p < 0.001) \), and in decreasing the average number of VPCs/hr by more than 70% (71% vs. 25% of patients) \( (p < 0.001) \) (62). The prevalence of silent myocardial ischemia on the follow-up 24-hour AECGs was insignificantly higher on no antiarrhythmic drug. However, silent ischemia was significantly abolished by propranolol, with 37% of patients with silent ischemia on their baseline 24-hour AECGs having no silent ischemia on their follow-up 24-hour AECGs \( (p < 0.001) \) (62).

Multivariate Cox regression analyses showed that propranolol caused a 47% significant reduction in sudden cardiac death \( (p = 0.01) \), a 37% significant decrease in total cardiac death \( (p = 0.003) \), and a 20% insignificant decrease in total death \( (p = 0.057) \) (Table 2) (62). Univariate Cox regression analysis showed that among patients taking propranolol, suppression of complex VA caused a 33% insignificant reduction in sudden cardiac death, a 27% insignificant decrease in total cardiac death, and a 30% insignificant reduction in total death (63). Among patients taking propranolol, abolition of silent myocardial ischemia caused a 70% significant decrease in sudden cardiac death \( (95\% \text{ CI}, 0.12–0.75) \), a 70% significant reduction in total cardiac death \( (95\% \text{ CI}, 0.14–0.56) \), and a 69% significant decrease in total death \( (95\% \text{ CI}, 0.18–0.53) \) (63).

There was also a circadian distribution of sudden cardiac death or fatal MI with the peak incidence occurring from 6 a.m. to 12 p.m. (peak hour was 8 a.m. and a secondary peak occurred around 7 p.m.) in patients treated with no antiarrhythmic drug (64). Propranolol abolished this circadian distribution of sudden cardiac death or fatal MI (64). In this study, propranolol also markedly reduced the circadian variation of complex VA (65) and abolished the circadian variation of myocardial ischemia (66).

In a retrospective analysis of the data from the CAST study, Kennedy et al. (67) found that 30% of patients with an LVEF of 40% or less were receiving \( \beta \) blockers. Forty percent of the patients were between 66 and 79 years of age. Patients on \( \beta \) blockers had a significant decrease in all-cause mortality of 43% at 30 days \( (p = 0.03) \), of 46% at one year \( (p = 0.001) \), and of 33% at two years \( (p < 0.001) \) (Table 2) (67). Patients receiving \( \beta \) blockers had a significant reduction in arrhythmic death or cardiac arrest of 66% at 30 days \( (p = 0.002) \), of 53% at one year \( (p = 0.001) \), and of 36% at two years \( (p = 0.001) \) (67). Multivariate analysis showed that \( \beta \) blockers were an independent factor for decreasing arrhythmic death or cardiac arrest by 40% \( (95\% \text{ CI}, 0.36–0.99) \), for reducing all-cause mortality by 33% \( (p = 0.05) \), and for decreasing occurrence of new or worsened CHF by 32% \( (95\% \text{ CI}, 0.49–0.94) \) (Table 2) (67).

ACE Inhibitors

ACE inhibitors have been demonstrated to cause a significant reduction in complex VA in patients with CHF in some studies (68,69) but not in other studies (70,71). ACE inhibitors
have also been shown to reduce sudden cardiac death in some studies of patients with CHF (32,72).

ACE inhibitors should be administered to reduce total mortality in older and younger patients with CHF (30,32,72,73), an anterior MI (31), an MI with an LVEF of 40% or less (28,29,32), and in all patients with atherosclerotic cardiovascular disease (23,33). ACE inhibitors should be used to treat patients with CHF with abnormal LVEF (30,32,72,73), or with normal LVEF (74,75).

On the basis of the available data, ACE inhibitors should be used in treating older or younger patients with VT or complex VA associated with CHF, an anterior MI, an MI with LV systolic dysfunction, or atherosclerotic cardiovascular disease if there are no contraindications to the use of ACE inhibitors. β Blockers should be used in addition to ACE inhibitors in treating these patients.

### Class III Antiarrhythmic Drugs

Class III antiarrhythmic drugs are potassium channel blockers, which prolong repolarization manifested by an increase in QT interval on the ECG. These drugs suppress VA by increasing the refractory period. However, prolonging cardiac repolarization and refractory period can trigger afterdepolarizations and resultant torsade de pointes.

In the Survival With Oral d-Sotalol (SWORD) trial, 3121 survivors of MI, mean age 60 years, with an LVEF of 40% or less were randomized to d-sotalol, a pure potassium channel blocker with no β-blocking activity, or to double-blind placebo (Table 3) (76). At 148-day follow-up, mortality was 5% in patients treated with d-sotalol versus 3.1% in patients treated with placebo (relative risk = 1.65; 95% CI, 1.15–2.36) (Table 3) (76). Presumed arrhythmic deaths accounted for the increased mortality (relative risk = 1.77; 95% CI, 1.15–2.74) (76). On the basis of these data, d-sotalol should not be used for the treatment of VT or complex VA in older or younger patients with heart disease.

#### Table 3  Effect of Class III Antiarrhythmic Drugs on Mortality in Patients with Heart Disease and Complex Ventricular Arrhythmias

<table>
<thead>
<tr>
<th>Study (Ref.)</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Waldo et al. (76)</td>
<td>At 148-day follow-up, mortality was 5.0% for d-sotalol vs. 3.1% for placebo (relative risk = 1.65; 95% CI, 1.15–2.36)</td>
</tr>
<tr>
<td>Julian et al. (77)</td>
<td>At 1-yr follow-up, compared with placebo, d,l-sotalol caused an insignificant reduction in mortality</td>
</tr>
<tr>
<td>Singh et al. (82)</td>
<td>Compared with placebo, amiodarone significantly suppressed VT and complex VA ($p &lt; 0.001$); 2-yr survival was not significantly different for amiodarone (69.4%) vs. placebo (70.8%)</td>
</tr>
<tr>
<td>Canadian Amiodarone Myocardial Infarction Arrhythmia Trial (83)</td>
<td>Amiodarone was very effective in suppressing VT and complex VA; at 1.8-yr follow-up, compared with placebo, amiodarone caused an 18% insignificant reduction in mortality</td>
</tr>
<tr>
<td>European Myocardial Infarct Amiodarone Trial (85)</td>
<td>At 21-mo follow-up, mortality was similar for amiodarone (13.9%) vs. placebo (13.7%)</td>
</tr>
<tr>
<td>Sudden Cardiac Death in Heart Failure Trial (86)</td>
<td>At 45.5-mo follow-up, compared with placebo, amiodarone caused a 6% insignificant increase in mortality, and implantable cardioverter-defibrillator therapy reduced mortality by 23% ($p = 0.007$)</td>
</tr>
</tbody>
</table>

*Abbreviations: VA, ventricular arrhythmias; VT, ventricular tachycardia; CI, confidence interval.*
Studies comparing the effect of d,l-sotalol, a class III antiarrhythmic drug with β-blocking activity, versus placebo or β blockers in patients with VT or complex VA have not been performed. In a study of 1486 patients with prior MI compared with placebo, d,l-sotalol did not significantly reduce mortality in patients followed for one year (Table 3) (77).

In the Electrophysiologic Study versus Electrocardiographic Monitoring (ESVEM) study, 74% of 486 patients were aged 60 years or older (78). In this study, Holter monitor-guided therapy significantly predicted antiarrhythmic drug efficacy more often than did the electrophysiologic study in patients with sustained VT or survivors of cardiac arrest (77% vs. 45% of patients). However, there was no significant difference in the success of drug therapy selected by the two methods in preventing recurrences of ventricular tachyarrhythmias.

In the ESVEM study, d,l-sotalol was more effective than the other six antiarrhythmic drugs (imipramine, mexiletine, pirmenol, procainamide, propafenone, and quinidine) used in reducing recurrence of arrhythmia, death from arrhythmia, death from cardiac causes, and death from any cause (79). However, 7 of 10 episodes of torsade de pointes during this study occurred in patients receiving d,l-sotalol (79). In 481 patients with VT, d,l-sotalol caused torsade de pointes (12 patients) or an increase in VT episodes (11 patients) in 23 patients (4.9%) (80). Women had a significantly higher risk for drug-induced VF.

On the basis of the available data, the use of β blockers is recommended over the use of d,l-sotalol in treating older or younger patients with VT or complex VA associated with heart disease.

Amiodarone is very effective in suppressing VT and complex VA associated with heart disease (81–83). Unfortunately, the incidence of adverse effects from amiodarone approaches 90% after five years of therapy (84). In the Cardiac Arrest in Seattle: Conventional Versus Amiodarone Drug Evaluation study, the incidence of pulmonary toxicity was 10% at two years in patients receiving an amiodarone dose of 158 mg daily (81). Amiodarone can also cause cardiac adverse effects, gastrointestinal adverse effects including hepatitis, hyperthyroidism, hypothyroidism, and neurologic, dermatologic, and ophthalmologic adverse effects.

A double-blind study randomized 674 patients with CHF and complex VA to amiodarone or placebo (Table 3) (82). Compared with placebo, amiodarone significantly reduced the number of episodes of VT \((p < 0.001)\) and the frequency of complex VA \((p < 0.001)\). Twenty-seven percent of patients discontinued amiodarone in this study. At two-year follow-up, survival was not significantly different in patients treated with amiodarone (69.4%) or placebo (70.8%) (Table 3) (82).

The Canadian Amiodarone Myocardial Infarction Arrhythmia Trial (CAMIAT) randomized 1202 survivors of MI with nonsustained VT or complex VA to amiodarone or placebo (Table 3) (83). Amiodarone was very effective in suppressing VT and complex VA in this study (Table 3) (83). Early permanent discontinuation of amiodarone for reasons other than adverse events occurred in 36% of patients taking this drug (83). At 1.8-year follow-up, amiodarone caused an 18% insignificant reduction in mortality (Table 3) (83).

The European Myocardial Infarction Amiodarone Trial (EMIAT) randomized 1486 survivors of MI with an LVEF of 40% or less to amiodarone or placebo (Table 3) (85). Early permanent discontinuation of amiodarone occurred in 38.5% of patients taking this drug. At 21-month follow-up, mortality was similar in patients treated with amiodarone (13.9%) or with placebo (13.7%) (Table 3) (85).

In the Sudden Cardiac Death in Heart Failure Trial (SCD-HEFT), 2521 patients, mean age 60 years, with New York Heart Association (NYHA) class II or III CHF due to ischemic or nonischemic heart disease, an LVEF of 35% or less, and a mean QRS duration on the resting ECG of 120 ms were randomized to placebo, amiodarone, or an
automatic implantable cardioverter-defibrillator (AICD) (Table 3) (86). At 45.5-month median follow-up, compared with placebo, amiodarone insignificantly increased mortality by 6% (Table 3) (86). At 45.5-month median follow-up, compared with placebo, AICD therapy significantly reduced all-cause mortality by 23% ($p = 0.007$), with an absolute reduction in mortality of 7.2% after five years (86).

Since amiodarone has not been found to reduce mortality in older or younger patients with VT or complex VA associated with MI or CHF and has a very high incidence of toxicity, β blockers should be used rather than amiodarone in treating these patients. A meta-analysis of 10 randomized trials showed that the use of β blockers significantly reduced two-year mortality in patients receiving AICD therapy ($p < 0.01$) (87). There are also data suggesting that patients receiving amiodarone plus blockers in the CAMIAT and EMIAT trials had a better survival than patients receiving amiodarone alone (88). Amiodarone plus a β blocker was also more effective than β-blocker therapy or sotalol in reducing AICD shocks for any reason (89).

INVASIVE INTERVENTION

If patients have life-threatening recurrent VT or VF resistant to antiarrhythmic drugs, invasive intervention should be performed. Patients with critical coronary artery stenosis and severe myocardial ischemia should undergo coronary artery bypass graft (CABG) surgery to reduce mortality (90). In the CABG Patch trial, there was no evidence of improved survival among patients with CAD, LVEF lower than 36%, and an abnormal signal-averaged ECG undergoing complete coronary revascularization and in whom an AICD was implanted prophylactically at the time of elective CABG surgery (91).

Surgical ablation of the arrhythmogenic focus in patients with life-threatening VT can be curative. This therapy includes aneurysctomy or infarctectomy and endocardial resection with or without adjunctive cryoablation based on activation mapping in the operating room (92–94). However, the perioperative mortality rate is high. Endoaneurysmorrhaphy with a pericardial patch combined with mapping-guided subendocardial resection frequently cures recurrent VT with a low operative mortality and improvement of LV systolic function (95). Radio frequency catheter ablation of VT has also been beneficial in the therapy of selected patients with arrhythmogenic foci of monomorphic VT (96–98). Catheter ablation has been very effectively used to treat patients with right ventricular outflow tract VT and LV fascicular VT.

AICD

However, the AICD has been widely accepted as the most effective treatment for patients with life-threatening VT or VF. Tresch et al. (93,94) showed in retrospective studies that the AICD was very effective in treating life-threatening VT in older as well as in younger patients. The Multicenter Automatic Defibrillator Implantation Trial (MADIT) randomized 196 patients, mean age 63 years, with a prior MI, an LVEF of 35% or less, a documented episode of asymptomatic nonsustained VT, and inducible nonsuppressible ventricular tachyarrhythmia on electrophysiologic study to receive an AICD or conventional medical therapy (Table 4) (99). Amiodarone was given to 74% of patients receiving conventional medical therapy versus 2% of patients receiving an AICD. β Blockers were given to 8% of patients receiving conventional medical therapy versus 26% of patients receiving an AICD. At 27-month follow-up, patients receiving an AICD had a 54% significant reduction in mortality (95% CI, 0.26–0.82) (99).
In the Antiarrhythmics versus Implantable Defibrillators (AVID) trial, 1016 patients, mean age 65 years, were randomized to an AICD or class III antiarrhythmic drug therapy (Table 4) (100). Forty-five percent of the patients had been resuscitated from near-fatal VF. The other 55% of the patients had sustained VT with syncope or sustained VT with an LVEF of 40% or less and symptoms suggesting severe hemodynamic compromise due to the arrhythmia (near-syncope, CHF, and angina pectoris).

Amiodarone was administered to 96% of patients randomized to medical therapy and to 2% of patients who had the AICD. Sotalol was administered to 3% of patients randomized to medical therapy and to 0.2% of patients who had the AICD. β Blockers were administered to 17% of patients randomized to medical therapy and to 42% of patients who had the AICD. The one-year survival was 89.3% for patients who had the AICD versus 82.3% for patients treated with drug therapy (95% CI, 39 ± 20% decrease in mortality) (Table 4) (100). The two-year survival was 81.6% for AICD versus 74.7% for drug therapy (95% CI, 27 ± 21% decrease in mortality); 3-year survival was 75.4% for AICD vs. 64.1% for drug therapy (95% CI, 31 ± 21% decrease in mortality).

The Canadian Implantable Defibrillator Study (CIDS) randomized 659 patients with VF, cardiac arrest, or hypotensive VT to an AICD or amiodarone therapy (Table 4) (101).
Cardiac arrhythmic mortality was 4.5% per year in patients treated with amiodarone versus 3% per year in patients treated with an AICD (risk reduction = 33%; \( p = 0.047 \)). Total mortality was 10.2% per year in patients treated with amiodarone versus 8.3% per year in patients treated with an AICD (risk reduction = 20%; \( p = 0.072 \)) (Table 4) (101). In a subset of CIDS, at 5.6-year follow-up, 47% of patients treated with amiodarone and 27% of patients treated with an AICD had died (102). Amiodarone caused adverse effects in 83% of patients receiving the drug (102).

The Cardiac Arrest Study Hamburg (CASH) randomized 230 patients surviving sudden cardiac death due to documented VT or VF to propafenone, metoprolol, amiodarone, or an AICD (Table 4) (103). Propafenone was stopped after 11 months because mortality from sudden death and cardiac arrest recurrence was 23% in patients randomized to propafenone versus 0% in patients randomized to an AICD (\( p < 0.05 \)) (Table 4) (103). The two-year mortality was 12.6% for 99 patients randomized to an AICD versus 19.6% for 189 patients randomized to amiodarone or metoprolol (37% reduction; \( p = 0.047 \)) (Table 4) (104).

The Multicenter Unsustained Tachycardia trial randomized 704 patients with inducible, sustained ventricular tachyarrhythmias to three treatment groups (Table 4) (105). Compared with electrophysiologically guided antiarrhythmic drug therapy, the five-year total mortality was reduced 20% by an AICD (95% CI, 0.64–1.01), and the five-year risk of cardiac arrest or death from an arrhythmia was reduced 76% by an AICD (95% CI, 0.13–0.45) (Table 4) (105). Neither the total mortality incidence nor the rate of cardiac arrest or death from arrhythmia was lower in patients randomized to electrophysiologically guided therapy and treated with antiarrhythmic drugs than in patients randomized to no antiarrhythmic treatment (105).

MADIT II randomized 1232 patients, mean age 64 years, with a prior MI and an LVEF of 30% or less to an AICD or to conventional medical therapy (Table 4) (106). \( \beta \) Blockers were given to 70% of AICD patients versus 70% of conventional medical therapy patients. ACE inhibitors were given to 68% of AICD patients versus 72% of conventional medical therapy patients. Statins were given to 67% of AICD patients versus 64% of conventional medical therapy patients. Amiodarone was given to 13% of AICD patients versus 10% of conventional medical therapy patients. At 20-month follow-up, compared with conventional medical therapy, the AICD reduced all-cause mortality from 19.8% to 14.2%, \( p = 0.016 \) (hazard ratio = 0.69; 95% CI, 0.51–0.93) (Table 4) (106). The effect of AICD therapy in improving survival was similar in patients stratified according to age, sex, LVEF, NYHA class, and QRS interval (106).

In MADIT-II, the reduction in sudden cardiac death in patients treated with an AICD was significantly reduced by 68% in 574 patients, younger than 65 years of age \(( p = 0.02)\), by 65% in 455 patients aged 65 to 74 years \(( p = 0.005)\), and by 68% in 204 patients aged 75 years or older \(( p = 0.05)\) (107). The median survival in 348 octogenarians treated with AICD therapy was more than four years (108).

After AICD implantation, 35 patients were randomized to treatment with metoprolol and 35 patients to treatment with d,l-sotalol (109). VT recurrence was 17% at one year and 20% at two years for patients treated with metoprolol versus 43% at one year and 49% at two years for patients treated with d,l-sotalol \(( p = 0.016)\). At 26-month follow-up, survival was 91% for patients treated with metoprolol plus an AICD, versus 83% for patients treated with d,l-sotalol plus an AICD \(( p = 0.287)\) (109). In MADIT-II, use of higher doses of \( \beta \) blockers in patients with ischemic heart disease and an AICD significantly reduced mortality by 56% to 58% compared with nonuse of \( \beta \) blockers \(( p < 0.01)\) (110). These data favor using a \( \beta \) blocker in patients with an AICD.
The American College of Cardiology (ACC)/American Heart Association (AHA) guidelines recommend that class I indications for therapy with an AICD are (1) cardiac arrest due to VF or VT and not due to a transient or a reversible cause; (2) spontaneous sustained VT; (3) syncope of undetermined origin with clinically relevant, hemodynamically significant sustained VT or VF induced at electrophysiologic study when drug therapy is ineffective, not tolerated, or not preferred; and (4) nonsustained VT with CAD, prior to MI, LV dysfunction, and inducible VF or sustained VT at electrophysiologic study that is not suppressed by a class I antiarrhythmic drug (111). We concur with these recommendations.

The updated ACC/AHA guidelines for treatment of CHF recommend with a Class I indication use of an AICD in (1) patients with current or prior symptoms of CHF and reduced LVEF with a history of cardiac arrest, VF, or hemodynamically destabilizing VT; (2) in patients with CAD at least 40 days after MI, an LVEF of 30% or less, NYHA class II or III symptoms on optimal medical therapy, and an expected survival of more than one year; (3) in patients with nonischemic cardiomyopathy, an LVEF of 30% or less, NYHA class II or III symptoms on optimal medical therapy, and an expected survival of more than one year; and (4) with a class IIa indication in patients with an LVEF of 30–35% of any origin with NYHA class II or III symptoms on optimal medical therapy, and an expected survival more than one year (112). We agree with these recommendations. An AICD should also be used in patients with CHF requiring cardiac resynchronization therapy (113).

An AICD may also be effective in preventing sudden death in patients with hypertrophic cardiomyopathy at high risk for sudden death (114), and in patients at high risk for sudden death because of a long QT interval or the Brugada syndrome (115). An AICD may be useful in preventing sudden death in patients with syncope and ventricular tachyarrhythmias associated with poor LV ejection fraction, regardless of the result of the electrophysiologic study (116). In addition, an AICD may be useful in survivors of VT or VF as a bridge to cardiac transplantation (117).

AICDs were implanted in 378 men and 95 women, mean age 69 ± 12 years (118). At 3.6-year follow-up, survival was 76% in patients who had an AICD because of cardiac arrest due to VF or VT and not due to a transient or reversible cause; 85% in patients who had an AICD because of spontaneous sustained VT in association with structural heart disease; 92% in patients who had an AICD because of syncope of undetermined origin with clinically relevant, hemodynamically sustained VT or VF induced at electrophysiologic study when drug therapy is ineffective, not tolerated, or not preferred; 84% in patients who had an AICD because of nonsustained VT with CAD, MI, LV dysfunction, and inducible VF or sustained VT at electrophysiologic study that is not suppressible by a class I antiarrhythmic drug; and 85% in all 473 patients (118).

AICDs are not effective in treating patients with LV dysfunction scheduled for elective CABG (91), or in patients who have had an acute MI within 40 days of the procedure (119). AICDs should also not be used to treat patients with NYHA class IV CHF despite optimal medical management or in patients with a life expectancy of less than one year (112).

In patients with AICDs, compared with patients treated with ventricular backup pacing at a rate of 40/min, patients treated with dual-chamber rate-responsive pacing at a rate of 70/min (DDDR-70) had an increase in mortality (120,121), worsening of LVEF (122), and an increase in new LV wall motion abnormality (122). One reason why DDDR-70 pacing may increase mortality and worsen LV systolic function is that ventricular electrical activation proceeds from the right ventricular apex instead of through the existing conduction system.
In patients with AICDs and no indication for antibradycardia pacing, 22 of 80 patients (28%) treated with right ventricular pacing died at 45-month follow-up, and 8 of 81 patients (10%) treated with biventricular pacing died at 53-month follow-up ($p < 0.01$) (123). At 23-month follow-up, the LVEF decreased from 36% to 30% in patients treated with right ventricular pacing and increased at 38-month follow-up from 35% to 40% in patients treated with biventricular pacing ($p < 0.001$) (123). New LV wall motion abnormality developed at 23-month follow-up in 23 of 80 patients (29%) treated with right ventricular pacing, and at 38-month follow-up in 7 of 81 patients (9%) treated with biventricular pacing ($p < 0.005$) (123). On the basis of the available data, patients with AICDs should be treated with biventricular pacing, not with DDDR-70 right ventricular pacing (120–123).

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Bradyarrhythmias and Cardiac Pacemakers in the Elderly

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DIAGNOSIS

Although the term bradycardia is used to describe any slow heart rhythm, usually under 60 bpm, it is always caused by specific abnormalities in cardiac impulse formation or conduction. Mean heart rates decline with age, but the prevalence and significance of bradyarrhythmias in the elderly remain controversial (1–6). Degenerative disease in the sinus node can lead to pathological sinus bradycardia, sinus arrest, or sinus exit block. Sick sinus syndrome is a condition that includes one or several abnormalities in sinus node or atrioventricular (AV) node function. AV block and block in the His-Purkinje system can occur as a result of ischemic heart disease or various degenerative processes. Baroreceptor and autonomic abnormalities can produce symptomatic sinus slowing or AV node block. Bradyarrhythmias are in the differential diagnosis of syncope and presyncope in the elderly. The identification of bradycardia as a cause of syncope is crucial because pacemaker therapy usually relieves the problem.

History

Bradycardia should be suspected in patients who present with symptoms of syncope, presyncope, episodes of light-headedness, or palpitations. Patients should be questioned about the relationship of these symptoms to time of day, activity, and position, since the causes of bradycardias are usually intermittent or precipitated by specific events. Often there are associated symptoms, such as dyspnea or chest pain, that can give a clue to the etiology of an arrhythmia. The patient should be asked to tap out any associated palpitations to help in differentiating rapid from slow and regular from irregular rhythms. If symptoms are associated with rapid palpitations, a bradycardia is unlikely to be an isolated cause of the patient’s complaints. However, tachycardias can end with a prolonged pause, which could produce syncope or presyncope. History of associated illness such as thyroid disease and use of sedative drugs or medications that can
produce bradycardia (such as β blockers, digoxin, calcium channel blockers, and certain sedatives or analgesics) should be elicited (7). Family members should be instructed to take the patient’s pulse during episodes, and to comment on the regularity and rate of the pulse.

Physical Examination

During an arrhythmia, pulse rate, rhythm, and blood pressure abnormalities may be detected. In addition, AV dissociation and variability of systolic blood pressure from beat to beat may give clues to the types of arrhythmia. The changes associated with AV dissociation may be seen as abnormalities in the venous pulse, such as intermittent high-volume A waves.

Electrocardiography

The findings obtained during history and physical examination may be nonspecific, and the diagnosis of symptomatic bradyarrhythmias rests with demonstration of the abnormality by electrocardiography (possibly with carotid sinus massage) and electrophysiological testing. Because of the intermittent nature of sinus node and conduction system abnormalities, a single 12-lead electrocardiogram (ECG) or a longer ECG rhythm strip is usually inadequate to make a diagnosis. Twenty-four-hour ambulatory (Holter) recordings should be obtained early in the evaluation of the patient. Careful evaluation of the rate and relationship of P waves and QRS complexes should be made. All pauses greater than 1.5 seconds on Holter monitoring should be examined to identify the mechanism of the event. In all cases, symptoms should be correlated with ECG abnormalities, and the patient should be instructed to keep a detailed diary of symptoms during the time of the Holter recording. Pauses of greater than two to three seconds may occur in normal individuals. If the event does not produce symptoms and is due to sinus node dysfunction, Mobitz type I AV block, or excess vagal tone, a pacemaker is not usually indicated. Lack of heart rate increase with exercise may be pathological and could result in presyncope.

In many individuals, 24- or 48-hours of Holter monitoring may be inadequate to identify symptomatic bradycardias. In these cases, a patient-activated event recorder or continuous memory loop recorder may be useful. Event recorders store several seconds or minutes of ECG data when an event button is activated. The stored tracing can be sent to a central location via telephone after the patient has recovered from the event. If episodes produce immediate syncope and do not allow the patient sufficient time to activate an event recorder, a memory loop recorder is more appropriate. These devices are more cumbersome since they remain on the patient for prolonged periods of time (up to 1 month or more), but for recording and correlating rare symptoms their use may be necessitated. A loop recorder monitors heart rhythm continuously, but memorizes a rhythm strip for a fixed interval of time before and after the patient (or bystander) presses a button to activate the device. Until recently, loop recorders required manual activation after an event took place. A looping device that autotriggers on slow, rapid, or irregular rhythms is now available for clinical use. Another monitoring service is available for difficult to diagnose cases; using wireless technology, a portable monitor immediately contacts a central facility staffed by trained observers who can make a diagnosis in almost real-time. In extreme cases, an implantable loop recorder that lasts up to 36 months (Medtronic Reveal™, Medtronic Corporation, Minneapolis, MN, U.S.) can provide diagnostic rhythm tracings with or without patient activation.
Provocative Testing

When the preceding techniques fail to provide a diagnosis, exercise testing, carotid sinus massage, head-up tilt table testing, or pharmacological testing can be employed. All such tests are generally insensitive and nonspecific, so they must be used in concert with other diagnostic tests. Failure of the sinus node rate to increase with exercise has been reported in sick sinus syndrome (8,9). An abnormally long pause during carotid sinus massage (greater than 3 seconds) may indicate hypersensitive carotid sinus reflex, but this may occur in asymptomatic elderly patients (10). Determination of intrinsic heart rate following autonomic blockade with propranolol and atropine may identify sinus node function that falls outside population-determined norms. Since all these tests fail to correlate abnormalities with symptoms, their usefulness is limited.

Electrophysiological Testing

The technique of electrophysiological testing can be useful in the diagnosis and management of a wide variety of atrial and ventricular arrhythmias (11). Pacing wires are inserted via a subclavian and/or femoral vein, with electrodes in the high right atrium and the right ventricular apex, and via the right femoral vein across the tricuspid valve with electrodes in the region of the Bundle of His (Fig. 1). Recordings are made from these sites and from other locations (e.g., the coronary sinus) as necessary. By analyzing conduction times, sites of block can be determined; by pacing the atrium and ventricle, the integrity of the conduction system can be studied and arrhythmias may be reproduced.

Figure 1 Surface ECG and intracardiac electrograms recorded during an electrophysiological study. Arrows show location of electrodes in the heart. I, II, V1—standard surface ECG leads. Abbreviations: ECG, electrocardiogram; HRA, high right atrium; HBE, His bundle electrogram; RVA, right ventricular apex; CS, coronary sinus; P–A interval, time from first atrial depolarization to lower atrial depolarization; A–H interval, time from lower atrial depolarization to His bundle depolarization; H–V interval, time from His bundle depolarization to first ventricular depolarization. The P–R interval is approximately equal to P–A + A–H + H–V intervals.
Sinus node function is usually evaluated during electrophysiological testing using sinus node recovery time and sinoatrial conduction time. The sinus node recovery time examines the ability of the sinus node to recommence firing after overdrive suppression with atrial pacing. A normal value in most laboratories is less than 1500 milliseconds. The measurement can be corrected for baseline sinus rate, in which case normal values range from 350 to 550 milliseconds. Sinoatrial conduction time is an indirect measurement of the time it takes for an impulse to travel into and then exit from the sinus node. The sensitivity of these techniques, even when combined, is only about 64%, with a specificity of about 88% (12).

Atrial conduction, AV node function, and His-Purkinje system function are assessed by measuring intracardiac conduction intervals and by atrial pacing. An electrophysiological study can be useful in identifying the site of AV block, and in assessing the competence of the His-Purkinje system at rest and during pacing.

An electrophysiological study should be performed in patients with suspected sinus node disease or AV block who are symptomatic with syncope or presyncope, and in whom the relationship between symptoms and a bradyarrhythmia has not been established. Patients who have symptoms documented to be due to bradyarrhythmias or patients with degrees of heart block that requires permanent pacing (see section on indications for cardiac pacing) do not require an electrophysiological study. When the site of AV block cannot be determined by electrocardiography or Holter monitoring and differentiation of the site would help in the decision to implant a pacemaker, a His bundle study should be performed. This study may be necessary in patients with a fixed 2:1 AV block and bundle branch block or in patients with a Mobitz type II block with a normal QRS in whom a block in the Bundle of His is suspected. The use of electrophysiological testing to diagnose patients with syncope of undetermined origin is discussed in chapter 20.

NORMAL CARDIAC CONDUCTION SYSTEM

The understanding of bradyarrhythmias and their management is enhanced by a knowledge of the normal cardiac conduction system (Fig. 2). Normal cardiac activation originates in a group of cells in the high right atrium, known as the sinus node. The node is composed of nodal cells, which are the source of normal impulse formation; transitional cells, which may form the pathway for impulse conduction to the atrium; and working atrial myocardial cells, which extend into the node from surrounding atrial tissue. The sinus node receives innervation from postganglionic adrenergic and cholinergic nerve endings. Adrenergic stimulation of β-1 receptors increases sinus rate by increasing the slope of diastolic depolarization. Vagal stimulation slows sinus node discharge and prolongs conduction times within the node through release of acetylcholine, which hyperpolarizes the cell membrane producing an increase in the time for the cell to reach firing threshold. From the sinus node, the normal cardiac impulse travels through atrial tissue and possibly through internodal and interatrial pathways, although this latter point is controversial (13,14). Conduction from the right to left atrium appears to travel preferentially over a band of muscle fibers known as Bachmann’s bundle.

The signal eventually reaches the AV node, located in the lower part of the right atrium near the septal leaflet of the tricuspid valve, anterior to the ostium of the coronary sinus. The AV node conducts the impulse from the atrium to the Bundle of His. In normal hearts, the remainder of the interface between atria and ventricles is electrically insulated. In patients with Wolff-Parkinson-White syndrome, this insulator and the AV node are short-circuited via a bypass tract known as the Kent bundle.
AV nodal tissue exhibits a characteristic known as decremental conduction: the more rapidly impulses stimulate and attempt to pass through the AV node, the more slowly the node will conduct, even to the point of intermittent block. Like the sinus node, the AV node is richly innervated by cholinergic and adrenergic nerve endings. Vagal stimulation increases AV node conduction time and can produce block. Sympathetic stimulation shortens AV node conduction time and refractory periods.

From the AV node, the cardiac impulse travels to the Bundle of His, the first part of the specialized ventricular conduction system. From the Bundle of His, the impulse travels through the bundle branches and eventually to terminal Purkinje fibers. These fibers form interweaving branches on the endocardial surface of both ventricles and allow rapid transmission of the impulse to the entire ventricular myocardium in a period of 60 to 100 milliseconds. Without the specialized ventricular conduction system, such as in bundle branch block, muscle conduction of the cardiac impulse requires longer periods of time, typically on the order of 120 to 160 milliseconds. This results in a prolonged QRS duration on the surface ECG. The anatomy of the bundle branches varies among individuals, although the most common configuration is that of a main right bundle branch and a left bundle branch that bifurcates into an anterior and a posterior fascicle.

Bradyarrhythmias can result from abnormalities in impulse formation in the sinus node or impulse conduction in the sinus node, atrial myocardium, AV node, Bundle of His, or bundle branches. Total or subtotal destruction of the sinus node or transitional zone tissue may be found in patients with sick sinus syndrome. Inflammatory and degenerative changes can also be seen in some cases. AV nodal block may be due to infiltration of the node by fibrosis or calcification from adjacent structures (Lev’s disease), like that in calcific aortic stenosis. The ventricular conduction system can be affected by degeneration caused by chronic ischemic heart disease or by a sclerotic degenerative process (Lenegre’s disease) (15).
SINUS NODE DYSFUNCTION

Sinus Bradycardia

Sinus bradycardia is defined as a sinus node rhythm with a rate of less than 60 bpm. The arrhythmia may result from excessive vagal tone or diminished sympathetic tone, medications such as β blockers, digoxin, or calcium channel blockers, or because of sick sinus syndrome and its associated anatomical abnormalities. Well-trained athletes can exhibit sinus bradycardia, but this is a less common cause in the elderly population. Sinus bradycardia can also occur during sleep, with manipulation of the eye during surgery, or secondary to hypothyroidism, hypothermia, intracranial tumors, meningitis, or increased intracranial pressure. Excessive vagal tone, as is seen during intense vomiting, can also produce symptomatic sinus bradycardia. Besides digoxin, β blockers and calcium channel blockers, lithium, reserpine, fentanyl, stadol, and clonidine have been reported to cause sinus bradycardia. β-Blocker eye drops may be absorbed and produce sinus slowing or AV node block (16,17).

The ECG during sinus bradycardia shows normal-appearing P waves before each QRS complex but occurring at a rate less than 60 bpm. Normal-appearing P waves imply that the impulse originates in the sinus node. There can be coexisting AV block that can further lower the ventricular rate.

Treatment of sinus bradycardia is usually not necessary unless the patient is symptomatic during the periods of slow rhythm. In the acute setting, such as following a myocardial infarction, symptomatic patients can be treated with 0.5 mg IV atropine, repeated every five minutes up to 2 to 3 mg. If atropine fails, an external transthoracic pacemaker or a temporary transvenous pacemaker should be employed. If temporary pacing is not available, consider cautious use of IV dopamine (5–20 μg/kg/min) or IV epinephrine (2–10 μg/min). Isoproterenol is no longer recommended because it can increase myocardial oxygen demand and is proarrhythmic even at low doses. If the patient exhibits chronic symptomatic sinus bradycardia not attributable to medications, permanent pacing is the treatment of choice.

Sinus Arrest

Sinus arrest occurs because of an abnormality in impulse formation caused by medications or any of the disease processes mentioned previously. Bradycardia occurs if lower pacemakers such as the AV node fail to produce an appropriate escape rhythm.

On the ECG, P waves are identified before each QRS and are normal in configuration, as they are in sinus bradycardia. The tracing shows a pause in the sinus rhythm, with a P–P interval that is not equal to a multiple of the patient’s basic P–P interval (Fig. 3). Treatment for asymptomatic sinus arrest is usually not required. For symptomatic patients, treatment is similar to that outlined for sinus bradycardia.

Sinoatrial Exit Block

Sinoatrial exit block represents an abnormality in impulse conduction from the sinus node to surrounding atrial tissue. It can be caused by medications, including type IA antiarrhythmic drugs such as quinidine and procainamide. The arrhythmia can also be caused by the other sinus node abnormalities described earlier. On the ECG, there is a pause in the sinus rhythm, which is equal to a multiple of the underlying P–P interval.
The treatment for patients with symptomatic sinoatrial exit block is similar to that for sinus bradycardia. For asymptomatic patients, no treatment is required and the block may be transient, resolving after any offending medications are discontinued.

**Sick Sinus Syndrome**

Sick sinus syndrome includes a number of abnormalities of the sinus node, atrial myocardium, and AV node. It is often considered synonymous with the bradycardia-tachycardia syndrome, which consists of paroxysmal regular or irregular atrial tachycardias alternating with episodes of bradyarrhythmias, but bradycardia-tachycardia is only one manifestation of sick sinus syndrome. Also included in the definition are persistent sinus bradycardia not caused by medications, episodes of sinus arrest or sinus exit block, abnormalities of sinus node and atrial function in conjunction with AV conduction abnormalities (such as atrial fibrillation with slow ventricular response), or any combination of these conditions (Fig. 4). The etiology of sick sinus syndrome is multifactorial, varying from patient to patient. There may be inflammatory or degenerative changes in the sinus node and perinodal tissues. Autonomic abnormalities are also common (18,19).

Treatment of sick sinus syndrome can be problematic, since medications used to suppress or slow down chronic or paroxysmal atrial tachycardias may exacerbate the associated bradycardias. Digoxin, in particular, can cause profound bradyarrhythmias in these patients. Often ventricular or AV pacing must be used with drug therapy to treat patients with the bradycardia-tachycardia syndrome.

**Figure 3** Sinus arrest. The escape beat is from the AV node, and the peaked T-wave following this beat implies that a P-wave is buried in the T-wave. *Abbreviation: AV, atrioventricular.*

**Figure 4** Long sinus pause after spontaneous conversion of atrial fibrillation to sinus rhythm in a patient with sick sinus syndrome. Prolonged recovery of the sinus node is characteristic of this condition and can also produce long pauses following electrical cardioversion.
Although prophylactic pacing is not indicated, patients who require digoxin, β blockers, calcium channel blockers, or antiarrhythmic medications should be monitored after these medications are started. If long ventricular pauses occur or if patients become symptomatic, they should receive permanent pacing.

CAROTID SINUS HYPERSENSITIVITY

Hypersensitive carotid sinus syndrome is defined as ventricular asystole greater than three seconds during carotid sinus stimulation, although the definition is arbitrary. Studies have shown conflicting results regarding the significance of the three-second pause during carotid sinus massage (20–22). Hypersensitive carotid sinus response can be found in elderly patients complaining of syncope or presyncope, but many of these patients have multiple causes for their symptoms.

The cause of hypersensitive carotid sinus syndrome is not known but may involve an abnormal baroreceptor set point, excessive release of acetylcholine, inadequate cholinesterase to metabolize the acetylcholine, or abnormal central autonomic response. Carotid sinus hypersensitivity may manifest clinically following carotid stimulation from head turning or from tight collars. On the ECG during carotid sinus stimulation, either sinus arrest or sinus exit block is found. Although AV node block can occur, it is infrequent because the sinus slowing usually masks its manifestation.

Atropine can blunt the cardioinhibitory effects of carotid sinus hypersensitivity, but long-term treatment requires ventricular pacing. Medications, such as β blockers, calcium channel blockers, digitalis, and clonidine, should be avoided in patients who do not have an implanted ventricular pacemaker. A study of 175 patients over the age of 50, who experienced an accidental fall without any other explanation and who had a greater than three seconds asystole during carotid sinus massage while supine or during 70° head-up tilt, found that patients randomized to receive a pacemaker had a 66% reduction in recurrent falls (23).

AV BLOCK

AV block is a nonphysiological delay in conduction or a lack of conduction of the electrical impulse from atria to ventricles. Block can result from abnormal conduction in any part of the electrical system of the heart. Blocks that occur during a period of time in which the AV conduction system should be refractory (e.g., an atrial premature contraction that occurs early after a normally conducted beat) must be excluded. The causes of block have been discussed previously and include ischemic heart disease, degenerative and infiltrative diseases, drug toxicities, and excess vagal activity. AV block can be paroxysmal or fixed. A patient can exhibit different degrees of AV block at different times and under different pathophysiological conditions.

Electrocardiographic criteria are used to define degrees of block. First-degree AV block refers to a delay in AV conduction without nonconduction. On the ECG, normal sinus P waves are followed by QRS complexes, but with a P–R interval that is prolonged at greater than 0.20 seconds. Occasionally, the P–R interval can be as long as one second. P–R interval prolongation can be due to slowed conduction in the atrium (prolonged P–A interval), in the AV node (prolonged A–H interval), or in the His-Purkinje system (prolonged H–V interval) (Fig. 1). The presence of a narrow QRS usually indicates disease in the AV node, but first-degree AV block with a widened QRS morphology does not localize disease to the AV node or the His-Purkinje system (24).
Second-degree AV block is manifested by intermittent lack of conduction from atria to ventricles. Mobitz type I second-degree AV block (also called Wenckebach block) is usually, but not always, due to disease in the AV node and produces a gradual prolongation of P–R intervals in successive beats until a P wave is completely blocked for one beat (Fig. 5). Mobitz type II second-degree block, which usually involves disease below the AV node in the His-Purkinje system, produces intermittent block in AV conduction without prior prolongation of the P–R interval (Fig. 6). Type I block is usually considered benign, since AV node disease is the usual site of block and the prognosis is good. There is lesser tendency for the process to progress to complete heart block and frank syncope.

Type I block can occur with inferior wall myocardial infarction and tends to be transient. Patients are generally asymptomatic and temporary or permanent pacing is not required. Type II block occurs more commonly after anterior wall myocardial infarction and usually indicates a large area of myocardial damage. Type II block also leads to complete heart block more frequently than type I and consequently produces more symptoms. Temporary and permanent pacing are usually indicated for type II block because of this propensity to advance to complete heart block. Following anterior wall myocardial infarction, mortality remains high despite permanent pacing because of the association with extensive myocardial damage.

There is a special case of second-degree block in which every other P wave is blocked. This is known as a 2:1 block. Since two successive P–R intervals cannot be examined, it is not possible to further classify the rhythm as type I (Wenckebach) or type II second-degree block from the surface ECG. When the QRS interval is narrow, the block is usually in the AV node. When the QRS interval is wide, the block can be in either the AV node or the His-Purkinje system. In such cases, it is necessary to examine long rhythm strips or 24-hours Holter recordings in an attempt to find evidence for Wenckebach or non-Wenckebach conduction.
The term “high-grade AV block” is used by many cardiologists but is not uniformly defined. Usually the term refers to a situation in which multiple consecutive P waves are blocked. Typically, the P–R interval does not change in conducted beats, so this rhythm resembles type II second-degree AV block.

In third-degree or complete AV block, there is a total lack of conduction and communication between atria and ventricles. The atrial rhythm does not affect the ventricular rhythm, which is produced by an escape focus in the AV node (junctional escape rhythm) or, more commonly, in the ventricle (idioventricular escape rhythm). The ECG during complete heart block usually exhibits three features: (1) nonconducted P waves; (2) AV dissociation (atrial and ventricular rhythms are independent); and (3) a regular ventricular response produced by the escape rhythm (Fig. 7).

An algorithm can be constructed to aid in the correct identification of the degree of heart block on the basis of the surface ECG (Fig. 8). By answering several simple yes–no questions, an accurate diagnosis can be established. One must first determine whether there are blocked P waves. If there are none and the P–R interval is greater than 0.20 seconds, the patient has first-degree AV block. If there are blocked P waves, then the P–R intervals must be examined. The algorithm does not require that an assessment be made of

**Figure 7** Third-degree (complete) AV block, with narrow complex escape rhythm (AV nodal escape). *Note: Notice the blocked P-waves, A–V dissociation, and regular ventricular response (from the escape rhythm).* **Abbreviation:** AV, atrioventricular.

**Figure 8** Algorithm for the ECG diagnosis of AV block. **Abbreviations:** AV, atrioventricular; ECG, electrocardiogram.
whether a particular P wave is causing a QRS; simply identify a QRS, find the P wave that precedes that QRS, and define that as a P–R interval. If the intervals are not variable, then the special case of second-degree block with a 2:1 conduction must be excluded. If a 2:1 conduction is present, it is not possible to further categorize the block as Mobitz type I or Mobitz type II, and the diagnosis of second-degree AV block, 2:1 is made. If the patient has constant P–R intervals and is not in a 2:1 block, then the diagnosis of second-degree AV block, Mobitz type II, is made. If the P–R intervals are changing and the ventricular rhythm is not regular, then the diagnosis of second-degree AV block, Mobitz type I, is present. If the ventricular response is regular, then the criteria for third-degree (complete) AV block have been met.

Electrophysiological testing can be used to identify the site of the AV block. In the nonmedicated state, the patient’s rhythm is recorded and the P–A, A–H, and H–V intervals are determined (Fig. 1). Lack of a His bundle depolarization following a blocked P wave signifies that the AV node is the site of the block. Presence of the His bundle signal following a blocked P wave indicates that the impulse has traveled through the AV node, has stimulated the Bundle of His, and has blocked below that point. Block below the Bundle of His generally requires permanent pacing.

First-degree block alone does not require treatment, except in patients with left ventricular dysfunction in whom a shorter AV interval results in hemodynamic improvement. Second-degree block, Mobitz type I, in an asymptomatic patient does not require treatment. Symptomatic Mobitz I can be treated acutely with temporary pacing and eventually with permanent pacing. A permanent pacemaker should be used only after possible causative medications have been discontinued. Permanent pacing is indicated in patients with symptomatic and asymptomatic Mobitz type II block. Patients who develop Mobitz II block during an acute myocardial infarction should probably receive a pacemaker, but even with permanent pacing, the mortality rate in this group of patients (especially those with anterior wall myocardial infarction) remains high. Acquired third-degree block requires permanent pacing, since the patient is dependent on an escape rhythm that may be unreliable. If the patient exhibits symptoms with complete heart block, a temporary pacemaker should be inserted while the patient waits for definitive therapy with a permanent pacemaker.

PACEMAKER THERAPY FOR Bradycardias

Indications

Guidelines for permanent pacemaker implantation have been developed by a joint committee of the American Heart Association, the American College of Cardiology, and the Heart Rhythm Society (formally the North American Society of Pacing and Electrophysiology—NASPE) (25), and the Health Care Financing Administration has published guidelines for reimbursement for pacemaker implantation. In general, permanent pacing is indicated to treat symptomatic bradyarrhythmias. If a causative drug can be identified and stopped, this should be done. Pacing should be undertaken only if the symptomatic arrhythmia persists. When symptoms cannot be temporally related to a bradyarrhythmia, controversies regarding indications for implantation exist.

Class I indications are those in which a permanent pacemaker is generally considered acceptable and necessary if the cause is not transient. These include third-degree and advanced second-degree AV block with symptoms (such as syncope, seizures, congestive heart failure, dizziness, or limited exercise tolerance) due to bradycardia; with
asystole more than three seconds or an escape rate less than 40 bpm; after catheter ablation of the AV node; after cardiac surgery; or secondary to certain neuromuscular diseases. Also included are type II second-degree AV block, intermittent third-degree AV block, alternating bundle branch block, certain second- or third-degree AV blocks following acute myocardial infarction, symptomatic bradycardia resulting from required long-term drug treatment without acceptable alternative drugs, bradycardia that leads to potentially life-threatening ventricular arrhythmias, sinus node dysfunction with documented symptomatic bradycardia or chronotropic incompetence, and recurrent syncope caused by carotid sinus hypersensitivity.

Class II indications include those in which there is some divergence of opinion. Class IIa indications are those in which evidence or opinion are in favor of usefulness, while class IIb indications are less well established. The class IIa indications for pacing include asymptomatic third-degree AV block with average ventricular rates of 40 bpm or faster; asymptomatic type II AV block with a narrow QRS; asymptomatic type I second-degree AV block localized in or below the Bundle of His; first- or second-degree AV block with signs or symptoms suggestive of pacemaker syndrome (e.g., dizziness, near syncope, confusion, heart failure, hypotension, fatigue, weakness, lethargy, light-headedness, pulsations in the neck, palpitations); syncope not demonstrated to be due to AV block when other causes have been excluded; syncope with sinus node abnormalities discovered at electrophysiological studies; syncope in a patient with hypersensitive carotid sinus response (>3 seconds of asystole); and neurally mediated syncope with bradycardia found on tilt table testing. Class IIb indications include marked first-degree AV block in patients with congestive heart failure in whom a shorter AV interval results in hemodynamic improvement; persistent second-degree or third-degree AV block following myocardial infarction; and minimally symptomatic patients with chronic heart rates of less than 40 bpm while awake.

Class III conditions are those in which pacing is not routinely indicated and scientific evidence cannot support its use. Such situations include asymptomatic first-degree or type I second-degree AV block; transient AV block that is expected to resolve; asymptomatic fascicular block; transient AV or fascicular block following myocardial infarction; sinus node dysfunction in asymptomatic patients; hypersensitive carotid sinus sensitivity in the absence of symptoms or in the presence of vague symptoms; and situational vasovagal syncope where avoidance behavior is possible and effective.

**Modes of Cardiac Pacing and Cardiac Pacemaker Codes**

The earliest cardiac pacemakers were simple devices that paced the ventricle or atrium and lacked the ability to sense the patient’s underlying heart rhythm. As the technology advanced, the ability to sense the patient’s native heartbeat was added, as was dual-chamber pacing. In the 1980s, multiprogrammability became common, allowing adjustments in many pacemaker parameters using an external programming device. Newer pacemakers have the ability to record certain details of pacemaker operation and electrograms during arrhythmic events. Most modern pacemakers can modulate their pacing rates independent of sinus node activity by using physiological sensors (such as activity, acceleration, minute ventilation, or QT interval). Some current pacemakers incorporate dual sensors. Pacemakers with two or more ventricular leads are being implanted to treat congestive heart failure, even in the absence of bradyarrhythmias (see chap. 20).

A pacemaker code system was developed by committees of the Intersociety Commission for Heart Disease Resources, the Heart Rhythm Society, and the British Pacing
and Electrophysiology Group (BPEG) (Table 1) (26). The code consists of at least three and up to five positions: the first identifies the chamber(s) paced; the second identifies the chamber(s) sensed; the third indicates the response of the pacemaker to a sensed event; the fourth indicates presence or absence of sensor rate modulation; and the fifth indicates the presence of multisite pacing (i.e., 2 leads in the atria or ventricles). Pacemakers with no sensing capabilities are identified as VOO or AOO. A ventricular demand pacemaker is designated VVI and, with rate modulation, VVIR (or VVIRO). The same pacemaker used in the atrium is designated AAI or AAIR. A pacemaker that senses atrial activity but only paces the ventricle following an atrial sensed event is designated VAT, or VDD with accompanying ventricular sensing (AV synchronous pacemaker). Such a pacemaker is useful in treating patients with complete heart block in whom sinus node activity is normal and can be used to modulate the ventricular pacing rate. A single pacing lead that provides atrial sensing (but not pacing) and ventricular sensing and pacing (VDD mode) is available from several manufacturers and reduces some of the cost and complexity of a two-lead system. Such pacemakers are not appropriate for patients with slow atrial rhythms since they cannot pace in the atrium. A pacemaker that paces both chambers but senses only the ventricle is designated DVI and is useful in patients with symptomatic sinus bradycardia in whom AV synchrony is desired (AV sequential pacemaker). A pacemaker that combines both dual-chamber pacing with dual-chamber sensing is designated DDD and is capable of tracking atrial activity and providing AV synchrony under all conditions. This is the most common dual-chamber mode used in modern pacemakers. Rate modulation in DDD pacing (DDDR) is useful in patients with an inadequate sinus node response to exercise. An interesting mode is DDI pacing, during which the pacemaker paces and senses both chambers but does not deliver a ventricular stimulation following a sensed atrial event. This mode (and DDDIR) is useful for patients with frequent atrial tachyarrhythmias in whom one wishes to maintain AV pacing when the patient is not in an atrial arrhythmia. DDDRV mode indicates DDD pacing, with rate response, in a patient with two or more leads in one or both ventricles (e.g., for congestive heart failure).

Dual-chamber pacing was once considered inappropriate for patients with frequent atrial tachyarrhythmias, in particular paroxysmal atrial fibrillation, because sensing of an atrial tachyarrhythmia would result in unwanted rapid ventricular pacing. However, newer pacemakers have the capability to switch modes from DDD to VVI, VVIR, DDI, or DDDIR during paroxysmal atrial tachycardias (27,28), thereby avoiding undesirable tracking of the arrhythmia. Consequently, the only absolute contraindication to dual-chamber pacing is chronic, continuous atrial fibrillation.

There are differing opinions regarding the relative benefits of dual-chamber over single-chamber pacing in the elderly population. In the Mode Selection Trial in Sinus

### Table 1 Pacemaker Codes

<table>
<thead>
<tr>
<th>Position I chamber(s) paced</th>
<th>II Chamber(s) sensed</th>
<th>III Response to sensed event</th>
<th>IV Rate modulation</th>
<th>V Multisite pacing</th>
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<tbody>
<tr>
<td>O = None</td>
<td>O = None</td>
<td>O = None</td>
<td>O = None</td>
<td>O = None</td>
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<tr>
<td>A = Atrium</td>
<td>A = Atrium</td>
<td>T = Triggered</td>
<td>R = Rate</td>
<td>A = Atrium</td>
</tr>
<tr>
<td>V = Ventricle</td>
<td>V = Ventricle</td>
<td>I = Inhibited modulation</td>
<td>V = Ventricle</td>
<td></td>
</tr>
<tr>
<td>D = Dual</td>
<td>D = Dual</td>
<td>D = Dual</td>
<td>D = Dual</td>
<td>(A + V)</td>
</tr>
<tr>
<td>(A + V)</td>
<td>(A + V)</td>
<td>(T + I)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>S = Single</td>
<td>S = Single</td>
<td></td>
<td></td>
<td>(A + V)</td>
</tr>
<tr>
<td>(A or V)</td>
<td>(A or V)</td>
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</tbody>
</table>
Node Dysfunction (MOST), dual-chamber pacing was associated with slightly more improvement in quality of life than was single-chamber pacing, but there was no difference in the combined end point of mortality and stroke, risk of atrial fibrillation was lower, and the incidence of heart failure hospitalizations was the same (29). In the Pacemaker Selection in The Elderly (PASE) trial, no difference in quality of life, death, stroke, or heart failure hospitalization was found between VVIR and DDDR pacing modes (30). In the Canadian Trial of Physiologic Pacing (CTOPP), patients with symptomatic bradycardia who received a dual-chamber pacemaker had a lower incidence of atrial fibrillation (5.3% vs. 6.6%), but no benefit in stroke or cardiovascular death, all-cause mortality, or heart failure hospitalizations (31).

One disturbing issue that has come to light in recent years is the potential for chronic right ventricular apical pacing to cause left ventricular dysfunction. Studies of ventricular versus atrial pacing in sick sinus syndrome patients demonstrated higher New York Heart Association (NYHA) class, and an increase in NYHA class in ventricular compared with atrial pacing (32,33). The Dual Chamber and VVI implantable Defibrillator (DAVID) trial showed that dual-chamber pacing increased mortality or hospitalization for congestive heart failure in patients with left ventricular systolic dysfunction and no conventional indication for pacing (34). Reasons for these observations are multiple including the effect of ventricular pacing on diastolic function, the production of paradoxical septal motion, the change in ventricular sequence of activation and its effect on ventricular remodeling and mitral regurgitation, possible increase in catecholamine levels with right ventricular apical pacing, and a decrease in cardiac output with ventricular versus atrial pacing (35). To minimize ventricular pacing in patients without third-degree AV block, several pacemaker companies have introduced devices with pacing modes that lengthen the AV delay to promote native conduction, essentially providing atrial (AAI) pacing with backup ventricular pacing (e.g., Medtronic AAI<>DDD mode).

Programming rate-modulated parameters is either done empirically or can involve the use of rate response tailoring, such as through some form of exercise testing, to achieve an optimum rate response prescription. Rate-modulated devices typically allow the physician to determine a threshold level for rate increase and a slope of heart-rate increase in response to the sensed physiological parameter.

Pacemaker Follow-Up

Although modern pacemakers and leads are extremely reliable, periodic evaluation of the pacemaker-lead-patient system is required. Initial thresholds for stimulation of the heart may change with time or with partial or complete dislodgment of the implanted leads. Follow-up is also required to predict impending battery depletion to allow for elective replacement of the pulse generator. Pacemakers are usually followed via some combination of trans-telephone monitoring and periodic patient visits. Medicare guidelines for pacemaker follow-up frequency, originally issued in 1984, are based on the demonstrated longevity of the particular pacemaker model being tested (Table 2). Most modern pacemakers meet the specifications for guideline II. There is no mandate that these recommendations be followed, but they provide a framework for establishing a follow-up schedule individualized to suit each patient. Patient symptoms or concerns may dictate additional ad hoc monitoring.

During a transtelephone-monitoring session, rhythm strips in the free-running mode and with magnet application are transmitted back to the receiving station at the physician’s office or commercial monitoring service. This testing allows for analysis of
pacemaker sensing, capture, and battery integrity, but usually does not give information about sensitivity or output thresholds. In-office testing involves a pacemaker interrogation and stimulation threshold testing. Most current pacemakers will report certain abnormalities, such as detected tachyarrhythmias, evidence of lead malfunction, and occurrences of mode switching (e.g., from DDD to VVI mode during paroxysmal atrial fibrillation). The follow-up also involves reassuring patients and answering questions that they or their family members may have regarding the pacemaker.

Future of Cardiac Pacing

The future promises devices with more sophisticated (but more “user-friendly”) programming capabilities, more reliable and more physiological metabolic rate sensors, and more capacity for providing useful telemetric information from the patient. Great strides are being made in the application of devices to the treatment of atrial and ventricular tachyarrhythmias using antitachycardia pacing, low-energy cardioversion, and high-energy defibrillation. At present, an implanted pacemaker is generally a contraindication to the use of magnetic resonance imaging (MRI), since all pacemakers and leads contain ferromagnetic components. In the future, it may be possible to develop pacemakers and leads that are totally nonferromagnetic, thus allowing patients to undergo MRI studies.

CONCLUSIONS

Bradycardias and the sick sinus syndrome, symptomatic and asymptomatic, are common in elderly individuals. Treating patients for such arrhythmias involves careful history taking, physical examination, and diagnostic testing. Correlating symptoms with
abnormalities of the rhythm can be challenging and, in some cases, impossible. However, such a correlation is important to allow proper therapy by medication and implanted devices. There is debate about the use of pacemakers for certain indications, but the demonstration of bradycardia-induced symptoms usually makes the decision straightforward.

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Cerebrovascular Disease in the Elderly Patient

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INTRODUCTION

Stroke is primarily a disease of the elderly. The incidence of stroke under age 65 is less than 2/1000/yr, but rises to 4.6/1000/yr for men and 3.8/1000/yr for women aged 65 to 74 years, and to 9.4/1000/yr for men and 7.4/1000/yr for women aged 75 to 84 years (1). Stroke is the third leading cause of death in the United States and is the leading cause of neurological disability. It is often felt to be a fate worse than death by elderly patients.

Stroke is caused by disruption of the circulation of blood to the brain, and can be ischemic due to occlusion of an artery or hemorrhagic due to rupture of an artery. Ischemia accounts for 80% to 85% of stroke while hemorrhage accounts for 15% to 20% (2,3). Ischemic stroke is caused primarily by atherosclerotic disease of large extracranial and intracranial vessels, occlusion of intracranial vessels by emboli from a cardiac source, and small vessel intracranial occlusive disease secondary to hypertension and diabetes (Figs. 1,2). Hemorrhage can be intraparenchymal in the brain itself, mainly from hypertension, or subarachnoid from rupture of an aneurysm arising from the vessels of the circle of Willis.

The major risk factor for cerebrovascular disease in studies of patients matched for other cardiovascular risk factors is hypertension (4). Diabetes (5) and cigarette smoking also play a significant role (6), while elevation of serum lipids is less consequential for cerebrovascular disease than for coronary artery disease (7). Control of these risk factors at a young age has contributed to an impressive reduction in the incidence of stroke in recent years, but addressing these risk factors in the elderly patient still plays an important role (1). Cardiogenic embolization, particularly from nonvalvular atrial fibrillation, assumes greater importance as an etiology for stroke in the elderly patient, and strategies have currently been developed to reduce the incidence of stroke in these patients (8).

While prevention of stroke is the principal goal in the treatment of patients with cerebrovascular disease, medical therapy for the elderly stroke patient can enhance outcome. New treatment modalities to restore cerebral circulation with thrombolytic therapy have changed the outlook on treatment of stroke, and therapeutic trials are under way to determine if neuroprotective agents can diminish the extent of irreversible brain damage in acute stroke.
The brain is supplied by an extensive interconnected network of arterial circulation. Each cerebral hemisphere receives blood flow from the ipsilateral internal carotid artery that branches into the middle cerebral artery over the lateral surface of the brain and the

**Figure 1** The anatomy of the cerebral circulation is diagrammed demonstrating the potential etiologies of ischemic stroke: cardioembolic, carotid atherothrombotic, intracranial atherosclerosis, and small vessel intracranial vascular disease. *Source:* From Ref. 2.

**Figure 2** The incidence of the various etiologies of ischemic stroke. *Source:* From Ref. 2.

**ANATOMY AND PHYSIOLOGY OF THE CEREBRAL CIRCULATION**

The brain is supplied by an extensive interconnection of arterial circulation. Each cerebral hemisphere receives blood flow from the ipsilateral internal carotid artery that branches into the middle cerebral artery over the lateral surface of the brain and the
anterior cerebral artery over the medial surface of the brain. The brain stem and cerebellum receive blood flow from the vertebral and basilar arteries, which terminate in the posterior cerebral arteries that feed the posterior portions of the cerebral hemisphere including the occipital and posterior parietal lobes and the thalamus.

Connections exist between the two carotid arteries through the anterior communicating artery and between the basilar artery and the two carotid arteries through the posterior communicating arteries. These collateral channels form a complete circuit of arterial supply known as the circle of Willis. Collateral circulation also can be provided by the external carotid artery that branches from the internal carotid artery at the bifurcation of the cervical common carotid. The external carotid artery can connect to the internal carotid circulation distally through the ophthalmic artery and through anastomoses between the meningeal branches of the external carotid artery and the surface branches of the cerebral arteries. Because of this collateral circulation, the brain can tolerate complete occlusion of a carotid artery without injury or symptoms, and there are case reports of patients with bilateral carotid artery occlusion and unilateral vertebral artery occlusion whose only symptoms are nonspecific dizziness (9).

Another protective mechanism for circulation to the brain is autoregulation. Blood flow is maintained constantly at an average of 50 to 70 mL/100 g/min in the gray matter containing neuronal cell bodies, and 10 to 20 mL/100 g/min in the white matter containing the neuronal axons at ranges of mean arterial blood pressure from 60 to 160 mmHg without fluctuations due to changes in pressure (10). Blood flow does fluctuate with the blood partial pressure of carbon dioxide (PCO2), increasing or decreasing by 4% per 1 torr of PCO2. This ensures that there will be increased blood supply to metabolically active regions of the brain that are producing large amounts of carbon dioxide so that sufficient oxygen can be delivered.

PATHOPHYSIOLOGY OF ISCHEMIC STROKE

Ischemic stroke is caused by thrombotic or embolic occlusion of arteries supplying the brain. Atherosclerotic disease at the cervical carotid artery bifurcation accounts for about 20% of ischemic stroke (1,2). Because of the extensive collateral circulation of blood to the brain, it is unusual for ischemic stroke to occur on a hemodynamic basis because of occlusive disease in the carotid or vertebrobasilar arteries, unless the channels through the circle of Willis are incomplete. Therefore, the primary mechanism for stroke due to occlusive disease at the carotid artery bifurcation is embolization of thrombus or atherosclerotic debris from plaque at the bifurcation, which occludes an intracerebral artery (11). With complete occlusion of the internal carotid artery (Fig. 3), thrombus can propagate distally in the artery and obstruct collateral channels, causing infarction of a large portion of the cerebral hemisphere. Infarction can sometimes occur on a hemodynamic basis because of hypoperfusion in watershed areas, which are supplied by the distal territories of two arterial trees such as the parietal lobe, which receives terminal branches from both the middle and posterior cerebral arteries. Watershed infarcts can also sometimes occur when there is hypoperfusion due to cardiac arrhythmia, syncope, or cardiac arrest (12).

Cardiogenic emboli present to the intracranial arteries account for 20% to 30% of ischemic strokes (1,2) (Fig. 4). The largest source of these emboli is thrombus from the left atrium in patients with atrial fibrillation, particularly in patients older than 75 years with a marked preponderance in women older than 80 years (8). Valvular heart disease, thrombus from akinetic ventricular wall with myocardial infarction or cardiomyopathy,
right-to-left shunts through a patent foramen ovale or atrial septal defect also contribute to cardioembolic stroke (1,2,13). Artery-to-artery emboli can also arise from atheromatous plaque at the arch of the aorta and may account for up to 4% of strokes (14,15).

Atherosclerotic occlusive disease of the large intracranial arteries is an unusual cause of stroke in white patients, but is more common in African-American and Asian patients (11). Intracranial thrombosis of small penetrating arteries supplying the deep structures of the brain, such as the internal capsule and basal ganglia, account for about 25% to 50% of ischemic strokes (1,2). These vessels are endarteries that do not have
collateral flow to the regions they supply. Thrombosis usually occurs because of proliferative thickening of the walls of these arteries due to fibrinoid necrosis or lipohyalinization caused by diabetes and hypertension (16). When these arteries occlude, they produce small holes in the deep white matter, often referred to as lacunes (16) (Fig. 5). While the lesions may be small, if they are located in significant white matter tracts such as the internal capsule, which carries the main motor and sensory fibers from the cerebral hemispheres, then a devastating neurological deficit such as complete paralysis of the contralateral arm and leg can result.

Unusual causes of stroke, such as vasculitis, hypercoaguable state from antiphospholipid antibody or protein C and protein S deficiency, arterial dissection, and hematologic abnormalities such as sickle cell disease occur mainly in younger patients and are less likely to occur in the elderly (17–21). Even with the advent of noninvasive imaging techniques to identify the nature and causes of ischemic stroke, in 5% to 10%
of strokes the etiology cannot be identified and these are classified as cryptogenic strokes (1,2).

Intracerebral hemorrhage usually involves the rupture of Charcot Bouchard aneurysm, a microaneurysm formed on the deep penetrating arteries and arterioles caused by hypertension (22). These hypertensive hemorrhages occur mainly in the deep structures of the brain in the region of the basal ganglia and external capsule (Fig. 6). In the elderly, more superficial hemorrhages into the lobes of the brain, lobar hemorrhages, become more frequent. Many of these lobar hemorrhages are still due to hypertension or can be hemorrhagic transformation of an embolic infarct (23). Another common cause of lobar hemorrhage in the elderly is amyloid angiopathy (Fig. 7), which can occur with or without coincident senile dementia of the Alzheimer’s type (24).

Subarachnoid hemorrhage can also occur in the elderly, but a demonstrable berry aneurysm is less frequent than in younger patients (25). There are reports of newly diagnosed arteriovenous malformations in elderly patients (26), but these are also a less common source of bleeding in the elderly than in younger patients.

**Figure 5** Multiple lacunar infarcts. Axial T2-weighted MRI sequence demonstrates multiple rounded areas of high signal intensity within the basal ganglia and thalamus (*arrowheads*). There is also an old infarct in the right frontal region (*hollow arrow*).
DIAGNOSIS OF STROKE

The symptoms and signs occurring with a stroke are determined by the anatomical location of the lesion. Most strokes involve the cerebral hemispheres with contralateral hemiparesis or sensory loss, loss of vision in the contralateral visual field, and behavioral and speech disturbances. Strokes involving the brain stem present with ipsilateral deficits of the cranial nerve function such as abnormality of eye movements and a contralateral hemiparesis. Dizziness is a common symptom in the elderly, but dizziness alone is rarely an indication of stroke unless it is accompanied by other signs of dysfunction in the region of the vestibular nuclei in the lateral medulla. Loss of sensation on the ipsilateral face and contralateral body, ipsilateral Horner’s syndrome and loss of gag reflex, and difficulty swallowing because of the involvement of the nucleus ambiguous supplying the vagus nerves are signs of lateral medullary infarction, known as Wallenberg’s syndrome. Ataxia is found with strokes in the cerebellum as well as the brain stem.

It is important to establish the etiology of the stroke because treatment regimens vary with different subtypes of stroke. The clinical history and physical examination and laboratory analysis are obtained to identify risk factors that could potentially have caused the stroke. The neurological examination is helpful in determining if there is an extensive lesion caused by the occlusion of a large vessel or a major hemorrhage, by determining if
there is alteration in level of consciousness along with the focal deficits involved. Lacunar strokes from occlusion of small vessels can also be diagnosed if the typical syndromes of pure motor stroke, pure sensory stroke, dysarthria clumsy hand syndrome, or ataxic hemiparesis are present in an alert patient (16).

The neck is auscultated with the stethoscope to detect a vascular bruit that could signify atherosclerosis at the carotid artery bifurcation as the cause of atheroembolic stroke. The blood pressure is taken to determine if there is hypertension, and the blood glucose is measured to determine if diabetes is present. An electrocardiogram is essential to document if arrhythmias such as atrial fibrillation are present that could predispose to cardioembolic stroke.
Computerized axial tomography (CAT scan) of the brain is usually performed initially to differentiate between hemorrhagic and ischemic stroke. Signs of infarction are often not visualized on CAT scan within the first 4 to 12 hours after ischemic stroke, and the CAT scan may have to be repeated after 48 hours to determine the location of the stroke. This is important to help differentiate whether the stroke was atherothrombotic or cardioembolic. Thrombotic strokes more frequently occur in the deep structures of the brain. Cardioembolic strokes usually occur by occluding major branches of the internal carotid artery such as the middle cerebral artery (27), producing an infarct in the discrete territory of the artery involved or by occluding distal branches resulting in cortical infarctions (Fig. 4). Magnetic resonance imaging (MRI) is more sensitive than CAT scan for detecting early signs of infarction in the first 4 to 12 hours, particularly when the technique of diffusion MRI is employed (Fig. 8) (28).

**Figure 8** Diffusion weighted MRI. A diffusion weighted MRI sequence demonstrates an acute infarct in the region of a previous middle cerebral artery territory infarction (*dark arrow*) as well as an acute watershed type infarct in the right parietal region (*curved arrow*). Abbreviation: MRI, magnetic resonance imaging.
The presence of a small, deep, lacunar infarct in a patient with diabetes and/or hypertension usually indicates that the stroke was caused by small vessel occlusive disease. A cortical infarct in a patient with a known cardiogenic source such as atrial fibrillation is usually sufficient to diagnose a cardioembolic stroke. Carotid duplex ultrasonography is usually performed in all patients with ischemic stroke to determine if atherosclerotic disease at the carotid artery bifurcation is the cause, since carotid occlusive disease can produce both superficial and deep cerebral infarction (29). Magnetic resonance angiography (MRA) can also be performed (Fig. 3) (30). Transcranial Doppler can identify occlusive disease of large intracranial arteries (31).

Transthoracic echocardiography is employed to rule out a cardiogenic source for stroke. If the suspicion is high that the patient had a cardioembolic stroke and no obvious source is identified, transesophageal echocardiography (TEE) is indicated. TEE is necessary to rule out thrombus in the atrium, right-to-left shunts in the heart such as patent foramen ovale or atrial septal defect, and plaque in the arch of the aorta (32–34).

**THERAPY OF ISCHEMIC STROKE**

The management of ischemic stroke is summarized in Table 1.

**Prevention of Ischemic Stroke**

At the present time, even with thrombolytic therapy, treatment is limited once an ischemic stroke has already occurred. The major goal for the management of cerebrovascular disease is prevention of stroke. Recent developments indicate that most strokes can be prevented, even when treatment is begun when the patient is already elderly, though early intervention is certainly preferable.

**Table 1** Management of Stroke

<table>
<thead>
<tr>
<th>Stroke subtype</th>
<th>Etiology</th>
<th>Therapy</th>
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<tr>
<td>Ischemic</td>
<td></td>
<td></td>
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<tr>
<td>Lacunar</td>
<td>Hypertension</td>
<td>Control of hypertension and diabetes</td>
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<td></td>
<td>Diabetes</td>
<td>aspirin, ticlopidine, tPA</td>
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<td>Cardioembolic</td>
<td>Atrial fibrillation</td>
<td>heparin, warfarin, aspirin, tPA</td>
</tr>
<tr>
<td></td>
<td>Cardiac valve thrombi</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Cardiac valve replacement</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Occult (PFO, ASD)</td>
<td></td>
</tr>
<tr>
<td>Large vessel</td>
<td>Atherosclerotic</td>
<td>Extracranial—aspirin, ticlopidine, tPA, carotid endarterectomy</td>
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<td>Intracranial—aspirin, warfarin, tPA</td>
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<td>Aneurysm</td>
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¹Question marks indicate controversial therapy.

*Abbreviations:* PFO, patent foramen ovale; ASD, atrial septal defect.
Control of Risk Factors

The modalities for prevention of occlusive cerebrovascular disease are similar to the strategies for prevention of coronary artery disease. Primary prevention is instituted in patients with the primary risk factors for cerebrovascular disease: hypertension, diabetes, atrial fibrillation, smoking, and elevated cholesterol. Secondary prevention is applied to patients who have had warning signs of occlusive cerebrovascular disease: auscultation of a cervical carotid artery bruit, transient ischemic attack (TIA) lasting up to 24 hours, transient monocular blindness (amaurosis fugax), reversible ischemic neurologic deficits (RIND) lasting over 24 hours, or mild stroke from which the patient is not significantly disabled.

Hypertension is the most significant risk factor for stroke. While prevention of stroke is more effective when treatment is started when the patient is young, it is also beneficial to treat hypertension in the elderly (35). Treatment of isolated systolic hypertension to a pressure below 160 mmHg with a thiazide diuretic and additional atenolol 25 mg as necessary (36) or with the calcium channel blocker nitrendipine significantly reduces the risk of stroke in the elderly (37). However, caution must be applied in treating elderly patients, since aggressive lowering of diastolic blood pressure below 65 mmHg may actually increase the risk of stroke. The risk of stroke is also increased with elevated diastolic blood pressure, and the lowest risk for stroke for elderly patients is in the range of 140/80 mmHg (38). The main factor for prevention of stroke is adequate reduction in blood pressure (39). There is evidence that the angiotensin-converting enzyme inhibitors ramapril and perindopril and the angiotensin-receptor blockers losartan and eprosartan confer an additional protective effect against stroke in addition to regulation of the blood pressure (40–43).

Diabetes causes proliferation of the walls of small arteries in the deep structures of the brain, which can lead to thrombosis (44). Strict control of blood sugar can prevent similar vascular changes observed in the retina (45) and probably does so in the brain as well, although it has never been definitively documented that strict control of blood sugar prevents ischemic stroke. Control of blood sugar may lessen the severity when a stroke occurs, because hyperglycemia at the time of a stroke increases the extent of infarction from an equivalent vascular occlusion (46). Ramipril has been used primarily to reduce the complications of diabetic nephropathy. Treatment with ramipril 10 mg per day reduced the risk of stroke by 33% for diabetic patients older than 55 years with at least one other risk factor for cardiovascular disease (40). Ramipril also reduces the relative risk of stroke by 0.68% in patients with evidence of vascular disease or diabetes plus one other cardiovascular risk factor with no reduction in cardiac ejection fraction or heart failure.

Serum lipids are not as significant a risk factor for stroke as they are for coronary heart disease, but reduction in serum cholesterol with the HMG coenzyme inhibitors simvastatin and pravastatin for prevention of myocardial infarction also reduces the incidence of stroke in coronary patients by 33% (47,48). Cholesterol reduction with atorvastatin has been shown to reduce the rate of recurrence of stroke by 33% in patients with an initial stroke (49). High dietary content of the antioxidants β carotene and vitamin E also have been shown to reduce the incidence of stroke, probably by prevention of propagation of atherosclerosis (50,51).

Maintenance aspirin therapy has been shown to be effective in prevention of myocardial infarction in asymptomatic elderly patients (52), and low-dose aspirin is commonly taken by the elderly on a daily basis. No definite similar reduction in the incidence of stroke in the well elderly patient has been documented with chronic maintenance aspirin therapy (52).
Cigarette smoking is a significant risk factor for stroke. Cessation of smoking reduces the risk of stroke to a level similar to nonsmokers after three years of abstinence. Elderly patients should still be encouraged to stop smoking.

MANAGEMENT OF PATIENTS WITH TIA

Platelet Antiaggregant Therapy

TIAs are a warning sign of impending stroke. About 25% to 33% of patients with TIA go on to have a completed stroke (53). The incidence of stroke can be reduced by 50% in male patients with TIA treated with the platelet antiaggregant aspirin 650 mg twice a day, but may not have been effective in women (54). Subsequent studies have demonstrated that lower doses of aspirin ranging from 30 to 325 mg significantly reduce the risk of stroke in both men and women (55–59), but that higher doses may be more effective than lower doses (60).

The platelet antiaggregant ticlopidine (Ticlid) was developed for patients who could not tolerate the gastrointestinal side effects of aspirin. Ticlopidine is actually a stronger platelet antiaggregant than aspirin. It blocks the adenosine diphosphate (ADP) receptor, which is close to the final common pathway for platelet aggregation (61), while aspirin inhibits thromboxane synthesis by cyclooxygenase (62). In a trial comparing aspirin 650 mg twice a day to ticlopidine 250 mg twice a day in TIA patients, ticlopidine conferred a 48% risk reduction of stroke after one year and 25% risk reduction after five years, compared with therapy with aspirin 650 mg twice a day (63). Subgroup analysis revealed that ticlopidine had an advantage over aspirin in women, African-Americans, and in prevention of lacunar type stroke from small vessel disease (64). However, in the African-American Stroke Study, ticlopidine did not show any advantage over aspirin therapy alone (65). Ticlopidine is now rarely used because it is associated with significant hematologic complications of leukopenia in 2% of patients (63) and thrombotic thrombocytopenic purpura in one of every 8000 patients (66).

Clopidogrel (Plavix) inhibits platelet aggregation by the same mechanism as ticlopidine, binding to the platelet ADP receptor, but does not have the hematological side effect profile of ticlopidine (67). Clopidogrel 75 mg a day has been shown to decrease the number of ischemic vascular events of all kinds by 8.7% compared with aspirin 325 mg a day in patients with atherosclerotic vascular disease including heart attack, peripheral vascular disease, and stroke (68). However, there was no significant reduction of recurrent stroke with clopidogrel in patients presenting with stroke as the initial event. The addition of aspirin 75 to 325 mg a day to clopidogrel has been shown to be useful in preventing recurrent myocardial ischemia in patients with acute coronary syndromes (69), but is not more effective than clopidogrel alone (70) or aspirin alone (71) for prevention of recurrent stroke. Clopidogrel has now virtually replaced ticlopidine for treatment of patients with TIA who cannot tolerate aspirin.

Dipyridamole prevents platelet aggregation by inhibiting the enzyme phosphodiesterase (72). Immediate release of dipyridamole has not been shown to be effective alone in preventing stroke in TIA patients (72) and did not appear to have an additive protective effect in combination with aspirin, compared with aspirin alone (72). A timed-release preparation of dipyridamole 200 mg twice a day reduced the risk of stroke in TIA patients by 18% compared with placebo, the same reduction as treatment with 50 mg of aspirin (73). The combination of aspirin 25 mg twice a day with this timed-release preparation of the platelet antiaggregant persantine (Aggrenox) 200 mg reduced the rate of stroke by 37% compared with placebo and 23% compared with aspirin (73). The efficacy of Aggrenox has
been confirmed in a second trial where there was a 20% risk reduction in recurrent stroke compared with doses of aspirin ranging from 30 to 325 mg a day (74). Aggrenox has a low side effect profile. Gastrointestinal symptoms are reduced with a low dose of aspirin. The only adverse reaction has been headache, which can be minimized by starting the drug once a day and increasing the dose to twice a day after one week. Therefore, Aggrenox appears to be a safe and effective drug for prevention of stroke in elderly TIA patients.

**Carotid Artery Disease**

Occlusive atherosclerotic disease at the carotid artery bifurcation is found in 50% of patients with TIA. In patients with TIA and less than 40% stenosis, carotid endarterectomy has been shown to be of no benefit compared with aspirin therapy 650 mg twice a day for prevention of stroke. A final resolution has not yet been determined for patients with 40% to 69% stenosis. For patients with 70% or greater stenosis of the internal carotid artery at the bifurcation ipsilateral to a TIA, surgical therapy has been shown to provide a 20% reduction in the incidence of subsequent stroke compared with medical therapy with aspirin in a center where the risk of the procedure itself is 2% or less (75).

Patients presenting with TIA are initially screened with ultrasonographic examination of the carotid bifurcation employing duplex sonography. The bifurcation is imaged with B-mode sonography to visualize atherosclerotic plaque (76). The degree of stenosis is determined by Doppler sonography, which measures the velocity of the red cells flowing through the artery by the change in frequency shift of the ultrasound, as it reflects back from the red cells as they go by (77). The velocity is increased as the lumen diameter narrows. Identification of stenosis greater than 70% can be obtained with about 90% accuracy compared to angiography (78).

If a stenosis of 70% or greater is established by duplex sonography, or if the results of the testing is not definitive, then MRA is performed to document the degree of stenosis (78). MRA also has an accuracy of 90% compared to angiography (78). When the results of the two studies agree, the accuracy is 99% (80). Performing these two noninvasive studies can avoid the risk of angiography, which can be as high as a 1% incidence of stroke, myocardial infarction, or death in patients with cerebrovascular disease (78). When the two studies do not agree, angiography is usually performed to determine if there is a greater than 70% stenosis, or to be certain that there is not an inoperable complete occlusion of the internal carotid. For patients who cannot have an MRA, CT angiography can be performed. This procedure also has a 90% accuracy compared with catheter angiography, but requires injection of a large volume of contrast dye, so that it may not be possible to perform on patients with congestive heart failure or renal disease.

Once the imaging procedures have documented a greater than 70% stenosis, the patient is usually treated with carotid endarterectomy unless there are outweighing medical contraindications to performing the surgery. For elderly patients who are not surgical candidates, stenting of carotid stenosis can be performed. The risk of stroke during the procedure is similar to that of carotid endarterectomy, but the systemic complications are reduced (79). The long-term efficacy of carotid stent has not yet been established. However, two recent studies have determined that there is a greater efficacy and lower complication rate with carotid endarterectomy than with carotid stenting in patients who are not at high risk for carotid endarterectomy (80,81).

The management of asymptomatic carotid artery stenosis remains controversial. The Asymptomatic Carotid Atherosclerosis Study (ACAS) documented a significant benefit of carotid endarterectomy, compared with medical therapy with aspirin 650 mg b.i.d. in patients with greater than 60% stenosis of the internal carotid artery (82). However,
the difference was small, with a 10% risk of stroke in the medical group compared with a 5% risk of stroke in the surgical group over a five-year-follow-up period. Furthermore, the results did not diverge until the fifth year of follow-up. This has implications for elderly patients because an immediate risk of complication of carotid surgery may outweigh a risk of stroke five years in the future, if the life expectancy of the patient is diminished by other illnesses. A more recent trial demonstrated a higher 16% reduction in stroke with carotid endarterectomy in patients with significant asymptomatic stenosis (83).

Several studies have indicated that acute proliferation of plaque with hemorrhagic changes and plaque growth are implicated in the etiology of thromboembolic events causing stroke from the carotid bifurcation (84–86). Since the overall incidence of stroke is low in asymptomatic patients, endarterectomy after the initial identification of asymptomatic carotid stenosis is usually reserved for patients with a very high-grade lesion or a plaque with large amounts of heterogeneous lucencies, suggestive of recent thrombus (85,86). The remaining patients can be followed with sequential duplex Doppler examinations every six months and endarterectomy performed if a progressive stenosis is identified (86,87) or if the patient becomes symptomatic with a TIA.

Prevention of Cardioembolic Stroke

The major risk factor for cardioembolic stroke in the elderly is nonvalvular atrial fibrillation (8). Patients younger than 70 years with atrial fibrillation but no other associated heart disease can be managed with aspirin to effectively prevent stroke (88–91). In elderly patients older than 70 years, all clinical trials for stroke prevention in patients with atrial fibrillation have shown that aspirin is ineffective in preventing embolic stroke due to atrial fibrillation, and anticoagulation with warfarin had a significant protective effect (88,90,92–94). In the Stroke Prevention in Atrial Fibrillation (SPAF) trial, the risk of hemorrhagic stroke and other hemorrhagic complications in the elderly over 75 years equaled the risk reduction of cardioembolic stroke induced by warfarin compared with aspirin (88). The degree of anticoagulation in the SPAF trial as measured by the international normalized ratio (INR) was higher than in the other trials of warfarin to prevent stroke in atrial fibrillation, in which a significant reduction in the number of ischemic strokes and poor outcomes was demonstrated (92–94). Therefore, the current recommendation is to treat elderly patients older than 75 years who have atrial fibrillation with warfarin for stroke prophylaxis, keeping the INR between 2.0 and 2.9, with a target of 2.5.

Cardioversion of patients with atrial fibrillation has been employed as a strategy to prevent cerebral emboli. However, these patients may still require anticoagulation. In the Atrial Fibrillation Follow-up Investigation of Rhythm Management (AFFIRM) trial, 3500 patients with atrial fibrillation, mean age 70 years, were randomized to treatment with rate control plus warfarin or maintenance of sinus rhythm plus warfarin. The incidence of stroke was 5.7% in the rate control group, compared with 7.3% in the sinus rhythm group. While this difference was not significant, 78% of the strokes occurred if warfarin was discontinued or the INR was below 2.0, indicating a continuing need for anticoagulation in these patients to prevent stroke (95).

Patients with mechanical cardiac valve replacements are generally treated with warfarin for prevention of embolic stroke with the INR maintained from 3.0 to 3.5 (96). Anticoagulation with warfarin has also been beneficial in preventing stroke during the first three months after myocardial infarction (97), although aspirin is usually used for long-term prophylaxis.

Patent foramen ovale is a major cause of cryptogenic stroke in the young, but does not play a major role as a cause of stroke in the geriatric population. There was no
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difference in the incidence of recurrent stroke in patients older than 60 years with patent
foramen ovale treated with either aspirin or warfarin (98).

Atherosclerotic plaque in the ascending aorta and aortic arch has also been
implicated as a potential source of cardioembolic stroke (34). When these plaques are
identified as an incidental finding with transesophageal echocardiography performed for
cardiac disease, then stroke prophylaxis should be instituted, although it has not been
documented whether aspirin therapy is sufficient, or anticoagulation with warfarin is
necessary. Recently, a technique has been developed to image aortic arch plaque with
transcutaneous duplex ultrasound, so that patients undergoing carotid duplex sonography
can be examined for aortic arch plaque as well (99).

Multi-Infarct Dementia

Elderly patients being evaluated for dementia are often found to have small infarcts or
ischemic changes on images of the brain with MRI and CAT scan (Fig. 5) (100).
Hypertensive patients have small lacunar infarcts in the deep structures, which may not be
causing any focal neurological deficits such as hemiparesis, but may cause or contribute
to cognitive decline. Patients with atrial fibrillation or other cardioembolic sources of
stroke may have silent infarcts that cause cognitive deficits without focal signs. Patients
with a history of stroke and mild focal neurological deficits may still have cognitive
disturbances. When ischemia is identified as a contributor to the dementia, identification
of stroke risk factors and vascular pathology is made and appropriate antithrombotic
therapy is instituted.

TREATMENT OF ACUTE ISCHEMIC STROKE

There are four objectives in the treatment of the acute stroke patient: (1) diagnosis and
prevention of medical complications that could be life threatening, (2) prevention of
progression of the current stroke, (3) prevention of recurrent stroke, and (4) reversal of the
symptoms of the current stroke.

Medical Complications

The major medical complications associated with stroke are myocardial infarction,
pulmonary emboli, aspiration pneumonia, and airway obstruction or reduction in the level
of consciousness that compromises respiration. Electrocardiogram is imperative to rule
out a concurrent myocardial infarction, and if there is any suggestive history, serial
enzymes are obtained. Stroke units with monitored beds are useful in detecting and
preventing complications of arrhythmia that could occur with concomitant myocardial
infarction, or as the result of the stroke itself. While echocardiographic changes of ST
segment depression, U waves, and ventricular fibrillation are more common with
hemorrhagic strokes, they can occur with large infarctions severe enough to produce
release of catecholamines that can injure the endocardium (101).

Patients who are immobilized from their strokes are treated with low-dose
subcutaneous heparin 5000 U b.i.d. or enoxeparin 30 mg q.d. to prevent thrombophlebitis.
If there is a substantial risk of bleeding, pressurized air boots can be used instead of low-
dose anticoagulation. If there is airway obstruction or obtundation interfering with
respiration, prophylactic endotracheal intubation is sometimes initiated. Observation of
the oxygen saturation with a pulse oximeter may be sufficient to determine when a patient
is becoming hypoxic and intubation is necessary. Patients are generally not fed when there is any obtundation or difficulty swallowing, usually for a period lasting 48 hours after acute onset of the stroke. However, if there is prolonged inability to swallow, a nasogastric tube or percutaneous gastric tube must be inserted to maintain nutrition for better recovery of the stroke patient.

Prevention of Progression

Prevention of progression of stroke is attained by careful monitoring of the patient. The blood pressure must be maintained at a sufficient level to insure perfusion of the ischemic penumbra, the region of brain around the core area of infarction that is ischemic but not irreversibly damaged. Most stroke patients have an elevation of the blood pressure for the first 48 hours, a response to the ischemic event, which resolves without treatment (102). If the blood pressure rises to a critical level over 200/120, moderate reduction with intravenous labetalol is employed to bring the pressure to the 180/100 range. Drastic reduction in blood pressure with agents such as nitroprusside can cause severe worsening of the stroke.

Progression of stroke can occur in both large vessel occlusive disease and in lacunar or small vessel occlusive disease. Administration of aspirin near onset of ischemic stroke has been shown to improve outcome (103). Acute intravenous anticoagulation with heparin or the low-molecular weight heparinoid Orgaron has not been effective in improving outcome in controlled clinical trials (104,105), although subcutaneous administration of low-molecular weight heparin has shown a small but significant beneficial outcome for stroke patients in one trial (106). Therefore, it is generally not necessary to anticoagulate all stroke patients acutely, while aspirin therapy should be instituted as soon as possible.

Patients with large vessel occlusive disease who show signs of evolving stroke may benefit from anticoagulation with heparin (107,108), particularly when there is brain stem infarction (109). However, the evolution of infarction must be the degree of extent of focal neurological findings, such as a worsening of limb weakness or new cranial nerve deficits. Decline in the level of consciousness of the patient without new focal deficits is common, particularly in patients with middle cerebral artery occlusion from cardioembolic stroke, who develop cerebral edema associated with reperfusion. In this instance, anticoagulation can be associated with adverse outcome because of the hemorrhagic transformation of the infarction and anticoagulation should not be administered. Anticoagulation should be employed judiciously in elderly patients older than 80 years who have a higher risk of hemorrhagic complications.

With mass lesions of the brain, corticosteroid medications such as Decadron and osmotic diuretics such as Mannitol are useful in reducing the amount of vasogenic edema surrounding the lesion. Acute administration of corticosteroids to all stroke patients has been shown to be of no benefit and may actually be deleterious to the patient’s outcome (110). In patients with reperfusion, vasogenic edema can develop, but the response to corticosteroids and osmotic agents is poor (111). These agents can have adverse consequences for stroke patients because the hyperglycemia associated with corticosteroids may cause exacerbation of infarction (48), and the dehydration associated with osmotic diuretics may cause reduced perfusion in the ischemic zone. Steroids have not been shown to be beneficial in preventing brain herniation in massive hemispheric strokes with edema. Mannitol 1000 g intravenously over one hour can be administered when herniation is imminent, particularly in cases of hyperperfusion with infarction following carotid endarterectomy (112). In extreme cases, hemicraniectomy of the skull on the affected side has been recommended to acutely relieve intracranial pressure and prevent herniation, but has been associated with long-term complications (113).
In some instances, brain stem stroke that is likely to progress can be diagnosed clinically when a pontine infarct is located rostral to the facial nerve nucleus, with ipsilateral face, arm, and leg weakness (114). This lesion usually involves the ventral anterior pons, where the pyramidal tracts carrying motor fibers from each cerebral hemisphere are located contiguously. Spread of infarction to both sides of the brain stem in this location can result in the locked-in state, where there is quadraparesis and inability to speak, but the patient remains fully conscious. This type of stroke is often associated with basilar artery occlusion and identification, and early heparinization of these types of patients may be beneficial in preventing worsening of the stroke. Carotid and transcranial ultrasound studies can be performed on acute stroke patients to identify large vessel occlusive disease in the carotid or vertebrobasilar circulation because these patients may benefit from early anticoagulation with low molecular heparin, although this has not been definitively established (115).

**Prevention of Recurrent Stroke**

Prevention of recurrent stroke is particularly important in patients with a cardioembolic source of stroke such as atrial fibrillation or cardiac valve replacement. These patients can have repeat embolization of clot from the heart (116). Cardioembolic stroke almost always causes red infarction, with petechial hemorrhage or hemorrhagic transformation of the infarct when reperfusion occurs with retraction of the embolic clot. Reperfusion usually occurs between 24 to 48 hours after the acute event. Early anticoagulation with heparin can lead to increased size of the hemorrhagic transformation with associated worsening of the neurological condition as well as coma and death from brain herniation. This is particularly applicable to elderly patients, as the risk of major hemorrhagic transformation increases with age (117,118).

In several studies, it has been determined that the risk of reembolization in patients with atrial fibrillation is about 2% while the risk of major hemorrhagic transformation resulting in clinical deterioration is about 8% in the first 48 hours after stroke (117,118). Early anticoagulation of stroke patients with atrial fibrillation with heparin or the low-molecular weight heparinoid Orgaron showed no benefit compared with placebo (105,119). Therefore, in patients with atrial fibrillation, anticoagulation is usually held for the first 48 hours, a CAT scan of the brain is repeated, and anticoagulation is initiated if the infarct is not very large and there is no hemorrhagic transformation. In the patients who do have large infarction or hemorrhagic transformation, it is usually safe to anticoagulate from 96 hours to one week following the acute stroke (120). A small area of infarction on the initial CAT scan does not indicate that it is safe to anticoagulate acutely because the full extent of the lesion may not be detected until up to 48 hours after the initial event. MRI, particularly with the diffusion weighted imaging technique, is more sensitive in identifying the full extent of early infarction, and when the region of ischemic brain on these studies is small, early anticoagulation can be instituted.

Early anticoagulation is also necessary in patients with prosthetic cardiac valves who break through with stroke because the risk of early reembolization is greater, particularly when noninfectious vegetations are seen on the prosthesis with echocardiography. However, bacterial endocarditis must be ruled out in these instances prior to anticoagulation because mycotic aneurysms can form from infected emboli and can cause hemorrhage when the patient is anticoagulated (121).

Long-term anticoagulation with warfarin can be started at the same time as acute anticoagulation with heparin to shorten the length of hospital stay. A loading dose of 10 mg per day for two days is started and subsequent doses are titrated to the prothrombin
time, unless the patient has demonstrated sensitivity to warfarin. As in patients with progressive stroke, anticoagulation should be performed judiciously in elderly patients older than 80 years because of a higher risk of hemorrhagic complications.

The International Stroke Trial demonstrated a beneficial effect of aspirin 300 mg orally given at the time of onset of ischemic stroke when outcome was analyzed after three months. A 1% reduction in poor outcomes was obtained, primarily from prevention of recurrent stroke. Subcutaneous heparin administration up to 12,500 units b.i.d. had a similar reduction in poor outcome from ischemic strokes, but this reduction was equaled by adverse hemorrhagic events associated with anticoagulation (122).

**Reversal of Stroke Symptoms**

Administration of the thrombolysin tissue plasminogen activator (tPA) intravenously at a dosage of 0.9 mg/kg over one hour with 10% given by bolus within three hours after the onset of stroke increases the number of patients with a good outcome from stroke after three months. As measured by functional scales, 31% of treated patients had improved outcome compared with 21% of placebo patients (123). There is an immediate improvement in 14% of the stroke patients administered tPA acutely, but there is a 3.6% rate of cerebral hemorrhage causing death, so that the overall difference within the first 24 hours between control and treated patients was not significant. However, after three months, the overall mortality rate is equal in treated and untreated patients. Tissue plasminogen activator can be administered safely to patients older than 80 years without an increase in the incidence of symptomatic cerebral hemorrhage, but the outcome of thrombolytic therapy is not as successful in the elderly as in younger patients (124).

Care must be taken in selecting patients for administration of tPA. To avoid hemorrhagic complications, the prothrombin time and partial thromboplastin time should not be elevated and the platelet count should not be reduced. The patient should not have a history of recent surgery or any other illness that could result in significant systemic bleeding. An unexplained anemia could indicate an occult source of bleeding and is also a contraindication for administration of tPA. Administration of intravenous tPA to patients more than three hours after ischemic stroke or to patients who have changes of infarction on CAT scan of the brain by the time they are ready for treatment leads to an unacceptable degree of hemorrhagic complications and should be avoided (125). Administration of streptokinase had a very high rate of hemorrhagic complications and is not employed in the treatment of acute ischemic stroke (126).

Either tPA or recombinant pro-urokinase (rpro-UK) can also be administered by intra-arterial catheterization directly to the occluded vessel under angiographic control. A randomized trial of 9 mg intra-arterial rpro-UK followed by heparin infusion was performed in 180 patients with middle cerebral artery occlusion treated within six hours after stroke. A favorable outcome occurred in 40% of 121 patients treated with rpro-UK and 27% of 59 patients treated only with heparin (127). The improvement in outcome was significant \( p = 0.04 \). Recanalization was also significantly improved to 66% in the treated group compared to 19% in the heparin group. However, the risk of symptomatic intracranial hemorrhage was 10% in the treated group compared with 2% in the heparin group. Intra-arterial thrombolytic therapy may be more valuable in vertebrobasilar occlusive disease when there are progressive symptoms and the expected outcome is so grave that it outweighs the risk of hemorrhagic complications (128). Clot retraction with the mechanical embolus removal in cerebral ischemia (MERCI) device has been approved for acute endovascular treatment of occluded intracranial arteries up to eight hours after stroke (129).
Another strategy that is under development for the treatment of acute ischemic stroke is the use of neuroprotective agents. Ischemia induces release of excitotoxic neurotransmitters, particularly glutamic acid. In the setting of ischemia, glutamate causes neuronal death by stimulation of the N-methyl-D-aspartate (NMDA) receptor, which induces lethal amounts of calcium to enter the neuron. In experimental animal models, administration of NMDA receptor antagonists protects neurons in the border zone of the infarct from irreversible ischemic necrosis, reducing the infarct volume and improving functional recovery (Fig. 9) (130). Several NMDA receptor antagonists have been examined in controlled treatment trials of ischemic stroke, but so far no significant improvement in outcome of stroke patients with these agents has been documented (131). Future studies

![Diagram of neurotransmitter release and receptor activation](image)

**Figure 9** The ischemic cascade induced by release of the excitatory amino acids, glutamate and aspartate, which stimulate the NMDA and AMPA receptors is diagrammed. Experimental therapeutic strategies include inhibition of release of the excitatory neurotransmitters (lamotrigine, riluzole), inhibition of sodium influx from stimulation of the AMPA receptor (APV, NBQX), and inhibition of calcium influx from stimulation of the NMDA receptor (aptiganel, dextorphan, memantine, selfatel, polyamines). Abbreviations: NMDA, N-methyl-D-aspartate; AMPA, α-amino-3-hydroxy-5-methylisoxazole-4-propionic acid; APV, ambulatory procedure visit; NBQX, 2,3-dihydroxy-6-nitro-sulfamoyl-benzo(f)-quinoxaline. Source: From Ref. 105.
may include reperfusion of the ischemic zone by administration of thrombolytic agents
followed by administration of neuroprotective agents to prevent ischemic neuronal
death.

The relative success of immediate treatment of stroke with tPA within three hours
after onset has altered the attitude about the management of stroke. Stroke now has to be
considered an emergency just like heart attack and is currently referred to as a brain
attack. Early recognition of stroke and emergency transport to a hospital facility capable
of acute management of stroke patients has become imperative.

**MANAGEMENT OF HEMORRHAGIC STROKE**

There are two types of hemorrhagic stroke, intracranial and subarachnoid. Intracranial
hemorrhage usually commences with severe headache and progressive focal deficit, often
leading to obtundation. Most intracranial hemorrhage is due to hypertension and involves
the deep structures of the brain around the basal ganglia and internal capsule (Fig 6) (22).
Hemorrhage into a superficial lobe in the brain is more common in elderly patients than
younger patients, partly due to amyloid angiopathy of the cerebral arteries (Fig. 7) (24).
Medical therapy of hemorrhage consists primarily of reduction in blood pressure in
hypertensive patients and supportive care. Endotracheal intubation may be necessary for
airway protection and for impending brain herniation with respiratory failure. Hyper-
ventilation may be helpful to reduce increased intracranial pressure. The osmotic diuretic
Mannitol can be administered at a dosage of 100 g intravenously to reduce cerebral edema
acutely in cases of impending herniation. There is no evidence that steroid medications
are of any benefit in improving the outcome of patients with intracranial hemorrhage
(132), but they are still occasionally employed for the individual case where reduction of
cerebral edema may be helpful. Decadron 10 mg intravenously, acutely followed by 4 mg
every six hours, is often used. Care must be taken to control blood sugar and prevent
gastrointestinal hemorrhage when administering steroid medications.

Surgical management of intracranial hemorrhage is employed in certain instances.
Shunting of fluid and removal of blood from the ventricular system can reduce intracranial
pressure and prevent hydrocephalus. Deep hemorrhages are usually not benefited by
surgical intervention, but occasionally improvement can be obtained with removal of lobar
hemorrhage (133,134). The one instance in which surgical management is generally
utilized is cerebellar hemorrhage, where drainage of the hematoma can be performed
without inordinate risk to prevent compression of the brain stem and death. Cerebellar
hemorrhage usually presents initially with dizziness and loss of balance along with
headache, progression of focal ataxic symptoms, and, often, somnolence and coma. Early
recognition of this condition can improve the outcome considerably with surgery (134).

**SUBARACHNOID HEMORRHAGE**

The major intracranial vessels are located in the subarachnoid space between the pia
mater and dura mater covering the brain. Aneurysms form primarily at branch points from
the vessels of the circle of Willis at the base of the brain. Rupture of these aneurysms
produces severe headache, photophobia, and stiff neck. The patient may become
somnolent or lapse into coma. A third nerve paralysis with ptosis, pupillary dilation, and
ophthalmoplegia can result when a hematoma forms on the oculomotor nerve running just
below the posterior communicating artery. Focal neurological disturbances such as
hemiparesis can also result acutely. Patients with mild-to-moderate deficits have a better
prognosis than patients with focal neurological deficit or stupor. CAT scan of the brain
can visualize subarachnoid hemorrhage in most cases, but sometimes lumbar puncture is necessary when the CAT scan is negative and there is a high clinical suspicion of subarachnoid hemorrhage. The aneurysm is identified by cerebral angiography.

The optimum care for subarachnoid hemorrhage is prevention of rebleeding by surgical clipping of the aneurysm or by thrombosing the aneurysm with endovascular coils. Surgery should be performed within the first 24 hours in patients with mild-to-moderate deficits. Surgical management after 24 hours is dangerous because of increased ischemic complications due to vasospasm. If surgery cannot be performed within the first 24 hours, it is usually deferred for up to 14 days (135). The ischemic consequences of spasm can be reduced by administration of the calcium channel blocker Nimodipine 60 mg orally every six hours (136,137). In some instances, the antifibrinolysin epsilon amino caproic acid is administered to prevent rebleeding when surgical therapy cannot be performed immediately, but is associated with an increase in ischemic complications (138). Spasm can be detected by measurement of increased flow velocities with transcranial Doppler, which can be employed to monitor patients for the onset of spasm after subarachnoid hemorrhage. When spasm occurs postoperatively, the blood pressure can be elevated to increase cerebral perfusion. Angioplasty can also be performed to dilate vessels when spasm is severe and is causing hemiparesis or stupor (139). When an elderly patient is at high risk for aneurysm surgery, endovascular placement of coils under radiological guidance can be employed to thrombose the aneurysm (140). A recent study demonstrated that coiling was safer and more effective than surgical management (141), but not all aneurysms are amenable to placement of a coil.

Arteriovenous malformations (AVM) of the brain, in which arteries feed directly into the venous system without going through a capillary bed, can also be a cause of subarachnoid hemorrhage. Surgical extirpation can be performed to eliminate the source of the bleeding, but often the AVM can recur or too much brain parenchyma is at risk for resection to be feasible (142). Embolization of colloidal particles or endovascular insertion of coils can be employed to thrombose the AVM. It is unusual to be able to eliminate the AVM by these methods, but the size can be reduced so that it becomes amenable to surgical removal. Radiosurgery with gamma knife technology can also be performed to eliminate or reduce the volume of the AVM (143).

CONCLUSION

New developments in the understanding of the pathophysiology of stroke and imaging technology for identifying the cause of stroke have dramatically changed the management of cerebrovascular disease. While the main focus remains prevention, new treatments with thrombolysis have changed the concept of stroke from a hopeless condition to a treatable disease. Further developments with neuroprotective agents hold the promise for further advancements in the treatment of stroke. The treatment of stroke as an acute emergency, a brain attack, has introduced a new era in the management of stroke, which can markedly alter the course of the disease in the elderly.

REFERENCES


Evaluation of Syncope in the Elderly Patient

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INTRODUCTION

Syncope is defined as a sudden transient loss of consciousness and postural tone with relatively rapid and spontaneous recovery. Transient cerebral hypoperfusion is the underlying pathophysiological event that results in syncope. The elderly are particularly vulnerable because of age-associated physiological changes in heart rate and blood pressure regulation, comorbid medical conditions such as hypertension and atherosclerosis, reductions in thirst, ability to preserve sodium and water as well as autonomic dysfunction, and the concurrent use of medications that affect blood pressure regulation.

Syncope is not, in and of itself, a disease; it is a symptom that can result from a wide variety of underlying pathophysiological processes. The assignment of a specific etiology can have profound effects on the prognosis and treatment of individual patients, but may be difficult to accomplish in practice. The differential diagnosis of syncope is extensive and spans a spectrum from common benign problems to severe, complex, and often life-threatening disorders. Another difficulty in evaluating elderly patients with syncope is the presence of multiple possible contributing factors. Patients older than 65 years have an average of 3.5 chronic medical comorbidities and use three times as many medications as younger patients. An analysis of elderly institutionalized adults with syncope suggested that 81% had two or more comorbid conditions that could have been implicated (1), and 25% of the elderly referred to an integrated “syncope clinic” for diagnosis were found to have two or more attributable conditions (2). Given the complexity of the differential diagnosis in the aged and the increased morbidity and mortality detailed below, it is not surprising that syncope often produces as much anxiety and frustration for medical professionals as for elderly patients and their families.
EPIDEMIOLOGY

The lifetime prevalence of syncope is 19% among the general population and higher among females than males (3). Large-scale population studies indicate that the incidence of syncope increases with age, rising most sharply after age 70 years. In the Framingham cohort, syncope was reported at 11.1 events per 1000 person-years in persons aged 70 to 79 years; in patients older than 80 years, the incidence of syncope was 16.9–19.5 events per 1000 person-years (4). The prevalence of syncope in very elderly (mean age 87 years) institutionalized patients is 23% over 10 years; the yearly incidence is estimated to be at least 6% in this group with a 30% recurrence rate (1). Eighty percent of emergency room patients evaluated for syncope are older than 65 years, and syncope accounts for 1% to 6% of all hospital admissions and 3% of all emergency room visits (5).

Data from the Framingham Heart Study (4) reveal that while the overall incidence rate of a first report of syncope was 6.2 per 1000 person-years, incidence rates increased with age, with a sharp rise at 70 years (Fig. 1). Additionally, among participants with cardiovascular disease the age-adjusted incidence rate was nearly twice that among participants without cardiovascular disease (10.6 vs. 6.4 per 1000 person-years).

Concomitant with rising prevalence and incidence of syncope with advancing age is the observation that a majority of older individuals admitted with syncope have functional limitations in several domains and would likely meet criteria for frailty, as has been demonstrated in other cardiovascular syndromes (6). Such noncardiac factors carry important, independent prognostic information and need to be considered in the development of an appropriate evaluation and treatment plan for a significant percentage of older individuals who are hospitalized with syncope.

Figure 1  Incidence rates of syncope according to age and sex. The incidence rates of syncope per 1000 person-years of follow-up increased with age among both men and women. The increase in the incidence rate was steeper starting at the age of 70. Syncope rates were similar among men and women.
IMPACT OF SYNCOPE

The consequences of syncope for the aging population are wide ranging, both on an individual and societal basis. Among older individuals presenting with syncope, the two-year mortality rate was 27% (7). Up to 30% of falls in the elderly may be due to syncope (8). Falls, either associated with syncope or even in the absence of loss of consciousness, can produce devastating injuries in the elderly. Five percent to 30% of falls in the community result in injury; approximately 5% of these are fractures and 1% are hip fractures. One in 40 community-dwelling elders who fall will be hospitalized. Only about half of these hospitalized patients will be alive one year after the fall (9). Unintentional injury is the fifth leading cause of death, and falls account for 70% of the accidental mortality among people older than 65 years. Even if no injury results, the fear of falling can be debilitating; elderly patients who fall often restrict their activities and show a higher incidence of depression and dependence in activities of daily living than their peers (10). The overall perception of health is proportional to the number of syncopal events in those with frequent recurrences (11), and such patients have impairment in their quality of life similar to those suffering from arthritis (12).

ETIOLOGIES AND THE IMPORTANCE OF RISK STRATIFICATION

The causes of syncope are traditionally broken down into several major etiological categories. We have found the following pathophysiological classification helpful: (1) primary cardiac arrhythmia (bradycardia or tachycardia); (2) structural cardiovascular disorder; (3) neurally mediated reflex disorders of blood pressure control; (4) orthostatic/dysautonomic disorders of blood pressure control; and (5) primary neurological or psychiatric diagnoses (Table 1). In a majority of the published studies, the term “cardiovascular syncope” is used to refer to the combined diagnoses of structural cardiovascular disease or primary cardiac arrhythmias, and will be so used here. The goals of diagnosing and treating patients with syncope are to reduce mortality and morbidity. In that vein, risk stratification for causes associated with excess mortality should be performed in all patients, and etiological diagnosis should be made to prevent morbidity associated with syncope recurrence by treating the underlying causes.

Unfortunately, the evaluation of syncope is often nondirected and costly, and frequently leads to great variability in practice and unsatisfying diagnostic conclusions. Examinations of current diagnostic strategies used in hospitalized elderly patients with syncope identified several relevant issues. Simple, inexpensive, and nonharmful evaluations are vastly underutilized; for example, postural vital signs were recorded in only 27% of one sample. Potentially high-yield provocative tests such as carotid sinus massage (CSM), tilt table testing (TTT) and electrophysiological study (EPS) are infrequently used, while at least one low-yield neurological study, such as carotid Doppler ultrasonography or head computed tomography (CT) scan, is obtained in nearly half of these patients. After an average length of stay of three to five days, 42% to 49% of cases remain undiagnosed (13,14). These results may be contrasted with the findings from trials investigating a standardized approach to syncope diagnosis in emergency room patients that indicate diagnostic efficiency of 76% to 83% (15,16). Indeed, a recent trial of a designated syncope unit in the emergency department for intermediate risk patients improved diagnostic yield in the emergency department and reduced the rate of hospital admission and the total length of hospital stay without affecting recurrent syncope and
### Table 1  Differential Diagnosis of the Causes of Syncope

<table>
<thead>
<tr>
<th>Primary Arrhythmia</th>
<th>Neurally mediated</th>
<th>Dysautonomia/orthostatic hypotension</th>
<th>Structural cardiovascular</th>
<th>Neurological/psychiatric</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tachyarrhythmias</td>
<td>Simple faint</td>
<td>Hypovolemia</td>
<td>Aortic dissection</td>
<td>Vertebrobasilar TIA</td>
</tr>
<tr>
<td>Ventricular including</td>
<td>Vasovagal</td>
<td>Medication-related</td>
<td>Atrial myxoma</td>
<td>Stroke</td>
</tr>
<tr>
<td>Ventricular tachycardia</td>
<td>Vasodepressor</td>
<td>Postprandial</td>
<td>Pulmonary embolus</td>
<td>Migraine</td>
</tr>
<tr>
<td>Torsades de pointes</td>
<td>Mixed phenotypes</td>
<td>Shy-Drager syndrome</td>
<td>Pulmonary hypertension</td>
<td>Seizure</td>
</tr>
<tr>
<td>Supraventricular tachycardia</td>
<td>Carotid sinus hypersensitivity</td>
<td>Parkinson’s disease</td>
<td>Subclavian steal</td>
<td>Narcolepsy</td>
</tr>
<tr>
<td>Atrial fibrillation/flutter</td>
<td>Situational</td>
<td>Spinal cord disease</td>
<td>Hypertrophic cardiomyopathy</td>
<td>Concussion</td>
</tr>
<tr>
<td>Bradyarrhythmias</td>
<td>Micturation</td>
<td>Diabetic neuropathy</td>
<td>Aortic stenosis</td>
<td>Panic attacks</td>
</tr>
<tr>
<td>Sick sinus syndrome</td>
<td>Cough</td>
<td>Amyloid</td>
<td>Mitral stenosis</td>
<td>Anxiety disorder</td>
</tr>
<tr>
<td>AV nodal block</td>
<td>Swallow</td>
<td>Other peripheral neuropathies</td>
<td>Pump failure</td>
<td></td>
</tr>
<tr>
<td>Sinus bradycardia</td>
<td>Defecation</td>
<td></td>
<td>Myocardial ischemia</td>
<td></td>
</tr>
<tr>
<td>Pacemaker malfunctions</td>
<td>Laugh</td>
<td></td>
<td>Pericardial disease/tamponade</td>
<td></td>
</tr>
<tr>
<td>Pacemaker-mediated tachycardia</td>
<td>Post-exercise</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Aortic stenosis
Evaluation of Syncope in the Elderly Patient

all-cause mortality. This change for the better reaffirms the importance of a systematic approach to evaluation (17).

A logical approach to diagnosis of syncope in the elderly patient begins with an understanding of the differential diagnosis and epidemiology (Table 2), although the true distribution of syncope etiology is difficult to determine because of the differences between populations studied and wide variance in strategies for evaluation. While many studies have examined the etiology of syncope in a variety of clinical settings, few specifically focus on patients older than 65 years or stratify their data by age range.

Studies often include patients with conditions other than true syncope, such as seizures or metabolic derangements. Many trials were performed prior to the common usage of testing modalities such as EPS and TTT and, consequently, the percentage of patients with an “unknown” etiology following evaluation is high in early studies. Nonetheless, some conclusions can be drawn from the available data. A large percentage of patients have orthostatic/dysautonomic or neurally mediated disorders of blood pressure control. Primary arrhythmias are fairly common, and structural cardiovascular disorders and primary neurological syncope are comparatively rare. These conclusions are supported by a large multicenter study in which a prospective systematic evaluation of consecutive patients referred to the emergency departments for syncope established a definite diagnosis in 98%, including neurally mediated syncope in 66% of diagnoses, orthostatic hypotension (OH) in 10%, primary arrhythmias in 11%, structural cardiac or cardiopulmonary disease in 5%, and nonsyncopal attacks in 6%, while only 2% were considered unexplained (18).

Data from cohort and prospective trials have revealed that syncope patients can be stratified into groups with high and low risks of death based on etiology. In a prospective study of 204 primarily hospitalized patients evaluated for syncope and followed for one year, the overall mortality rate was 30% and the rate of sudden death was 24% in patients with a cardiovascular cause as compared with 12% and 4%, respectively, in patients with a noncardiovascular etiology (19). In the Framingham cohort, patients with isolated syncope (i.e., syncope in the absence of prior or concurrent neurological, coronary, or other cardiovascular disease stigmata) did not suffer from excess all-cause or cardiovascular (including sudden death) mortality (20). Similarly, an examination of a community-based sample from the Framingham cohort (average age 66 years) indicates that the excess mortality in patients with syncope is attributable almost entirely to those with a cardiovascular etiology [adjusted hazard ratio for mortality of 2.01; 95% confidence interval (CI) 1.48–2.73], while subjects with neurally mediated, medication-related, or orthostatic/dysautonomic syncope (45% of the sample) did not show increased mortality (adjusted hazard ratio of 1.08; 95% CI 0.88–1.34) (4). A prospective multivariate analysis comparing 940 relatively young (mean age 52.5 years) patients with similar cardiovascular disease severity on a symptom scale, with and without syncope, suggested that mortality was related to underlying cardiac disease severity much more strongly than to the incidence of a syncopal event itself (21).

INITIAL WORKUP

The initial diagnostic workup should consist of history, physical examination, and 12-lead electrocardiography (ECG). Studies across a wide range of subjects indicate that the history and physical examination alone can directly make a diagnosis in up to 50% of patients with syncope, and can suggest possible etiologies in many more. The ECG makes
Table 2  Epidemiology of Syncope in the Elderly Patient

| Study design (investigators) | Date (Ref.) | N | Mean age | Clinical setting | Primary arrhythmia | Structural cardiovascular | Neuromedi mediated | Orthostatic — dysautonomic, drug-related | Primary neurological psychiatric | Unknown, other unspecified |
|-----------------------------|-------------|---|-----------|------------------|-------------------|--------------------------|-------------------|-----------------|-------------------------------|---------------------|-------------------------|
| Lipsitz et al. (retrospective) | 1985 (1)    | 67 | 87       | Nursing home     | 3 (4%)            | 10 (15%)                | 11 (16%)          | 15 (22%)         | 7 (10%)                        | 21 (31%)             |
| Kapoor et al. (prospective)  | 1986 (6)    | 210 | 71       | ED, in-patients  | 54 (26%)          | 14 (7%)                  | 25 (12%)          | 25 (12%)         | 10 (5%)                        | 83 (40%)             |
| McIntosh et al. (prospective) | 1993 (2)    | 65 | 78       | Syncope clinic   | 14 (21%)          | 0 (0%)                   | 37 (56%)          | 21 (32%)         | 12 (18%)                       | 10 (15%)             |
| Getchell et al. (prospective) | 1999 (12)   | 1516 | 73      | In-patients      | 217 (14%)         | 67 (4%)                 | 193 (13%)         | 254 (17%)        | 69 (5%)                        | 716 (47%)            |
| Ammirati et al. (prospective) | 1999 (14)   | 195 | 63       | ED               | 35 (18%)          | 6 (3%)                  | 69 (35%)          | 12 (6%)          | 38 (20%)                       | 35 (18%)             |
| Soteriades et al. (prospective) | 2002 (3)    | 822 | 66       | Community        | 78 (10%)          |                        | 174 (21%)         | 133 (16%)        | 74 (9%)                        | 363 (44%)            |

**Abbreviation:** ED, Emergency department.

*Percentages add up to more than 100% because some subjects were found to have multiple causes of syncope.*
Evaluation of Syncope in the Elderly Patient

a definitive diagnosis in only a few patients, but is helpful in identifying patients likely to have underlying structural heart disease and/or cardiac conduction disturbances (22). Laboratory tests are rarely definitive and probably can be limited to those patients in whom a particular disorder (anemia, hypoglycemia, severe dehydration) is suspected as a contributing factor.

Patient History

In evaluating patients, it is essential to differentiate syncope from other entities. Conditions such as vertigo, substance intoxication, and hypoglycemia that do not result in a transient loss of consciousness with spontaneous recovery are not syncope. Sustained arrhythmic events requiring electrical or chemical cardioversion present with a spectrum of clinical events ranging from syncope to sudden cardiac death; in these cases the diagnosis is usually not in question, and the evaluation strategy to follow is clear.

Seizures are another common cause of unexplained loss of consciousness, but also do not constitute true syncope. Distinguishing between syncope and seizure is a common diagnostic problem, but can usually be accomplished from the history. It should be noted that many patients with syncope have myoclonic jerks that can be mistaken for seizure activity by witnesses. In one series of patients with neurally mediated syncope during TTT, 8% of patients with positive tests had apparent neurological events (23). In a study of 94 consecutive patients who had transient loss of consciousness, the best discriminatory finding was orientation immediately after the event according to the eyewitness. Nausea and sweating before the event were useful to exclude a seizure but, contrary to common clinical teaching, incontinence and trauma were not discriminatory findings (24). Another study found that lateral tongue biting had a sensitivity of 24% and a specificity of 99% for the diagnosis of generalized tonic-clonic seizures (25). A standardized evaluation of 671 patients with loss of consciousness revealed head turning and unresponsiveness during unconsciousness to be predictive of seizures, while dizziness or diaphoresis prior to the event or loss of consciousness after prolonged sitting or standing were suggestive of syncope (26). In addition, patients with seizures often have a history of prior seizures or other neurological symptoms or findings on neurological examination that suggest the diagnosis.

Distinguishing between syncope and falls can be difficult. The traditional view considers these entities as two separate syndromes, often with separate etiologies, but there is considerable clinical overlap in the elderly. Discriminating between syncope and falls relies upon accurate accounts from patients and/or witnesses of the event. Classically, patients postsyncope recall the circumstances and events immediately preceding loss of consciousness (LOC), possibly up to the initial loss of postural tone, and then recall finding themselves on the ground after the gap in consciousness but, unlike patients with simple falls, they cannot recall actually striking the ground. In contrast, patients with simple falls complicated by transient LOC due to head trauma (i.e., concussion) should distinctly recall striking their head before blacking out.

Unfortunately, many elderly patients have retrograde amnesia regarding the event; one study demonstrated that 32% of cognitively normal older adults could not remember falling three months afterward (27). Other trials have shown that 21–32% of subjects with witnessed syncope during CSM have amnesia for the loss of consciousness (28,29). A witnessed account is unavailable in many cases of falls brought to medical attention. Falls not resulting from an obvious cause, such as impaired gait or balance with a resulting slip or trip, often have an attributable cardiovascular cause, particularly bradycardia or neurally mediated blood pressure control disorders (23). Thus, in the elderly, syncope and
unexplained falls may be indistinguishable clinical manifestations of the same pathophysiological process, and for this reason we treat any unexplained fall in an elderly adult as potential syncope.

Once it has been established that the patient has had syncope, the primary history taking should focus on precipitating factors, prodromal symptoms, and symptoms following the event. Chronology of recurrence, if applicable, can aid in evaluation. Parallel history attained from a reliable witness is often invaluable.

Historical factors associated with particular etiologies of syncope are detailed in Table 3. Nausea, warmth, diaphoresis, and lightheadedness are typical prodromal factors associated with neurally mediated syncope, but elderly patients commonly experience syncope without a prodrome. Residual symptoms are uncommon in patients with arrhythmia-induced syncope, while those with neurally mediated disorders of blood pressure control may describe moderate-to-severe fatigue afterward (30). A thorough evaluation of cardiovascular symptoms (i.e., angina, dyspnea, edema, and exercise intolerance) should be obtained in all patients. In patients with suspected or known structural heart disease, the most specific historical elements for cardiovascular syncope are syncope while supine or during exertion, blurred vision, and duration of symptoms less than four years. In patients without suspected heart disease, palpitations are the only

<table>
<thead>
<tr>
<th>Table 3</th>
<th>Historical Factors Associated with Various Etiologies of Syncope</th>
</tr>
</thead>
<tbody>
<tr>
<td>Historical feature</td>
<td>Associated diagnosis</td>
</tr>
<tr>
<td>Nausea, diaphoresis, warmth, long prodrome, total duration of episodes greater than 4 years</td>
<td>Neurally mediated syndrome</td>
</tr>
<tr>
<td>Absence of cardiovascular disease</td>
<td>Neurally mediated syndrome</td>
</tr>
<tr>
<td>Nausea or vomiting associated with syncope</td>
<td>Neurally mediated situational syncope</td>
</tr>
<tr>
<td>Syncope occurs after sudden, unexpected, or unpleasant sight, sound, smell, or paint</td>
<td>Neurally mediated situational syncope</td>
</tr>
<tr>
<td>During or after micturition, defecation, coughing, laughing, swallowing</td>
<td>Neurally mediated situational syncope</td>
</tr>
<tr>
<td>Syncope occurs during a meal or in the absorptive state after a meal</td>
<td>Postprandial hypotension</td>
</tr>
<tr>
<td>With neck pressure (tight collar, shaving, head turning)</td>
<td>Carotid sinus hypersensitivity</td>
</tr>
<tr>
<td>Postepisode confusion, lateral tongue biting, head turning during episode</td>
<td>Seizure</td>
</tr>
<tr>
<td>Diplopia, ataxia, vertigo, dysarthria</td>
<td>Neurological (transient ischemic attack, migraine, stroke) or subclavian steal</td>
</tr>
<tr>
<td>With arm exercise</td>
<td>Subclavian steal</td>
</tr>
<tr>
<td>Upon assuming upright posture or after prolonged standing, especially in crowded or hot places</td>
<td>Orthostatic hypotension</td>
</tr>
<tr>
<td>During or after exertion</td>
<td>Aortic stenosis, myocardial ischemia, vasodepressor response to exercise</td>
</tr>
<tr>
<td>While supine</td>
<td>Arrhythmia</td>
</tr>
<tr>
<td>History of myocardial infarction or congestive heart failure</td>
<td>Arrhythmia</td>
</tr>
</tbody>
</table>
predictor of a cardiovascular etiology (31). Particular attention should also be paid to the use of vasodilating, antiarrhythmic, diuretic, or bradycardic medications.

Despite the wealth of data demonstrating the value of historical information in guiding the diagnostic and management strategy for patients with syncope, the medical history has a reduced diagnostic specificity in older individuals. In one study, the diagnosis of the cause of syncope was possible on the basis of the history alone in 26% of younger patients and 5% of older patients, with older individuals having fewer prodromal symptoms and signs (32).

Physical Examination

A detailed physical examination should be performed in all patients with syncope. Hydration status and orthostatic changes in vital signs should be assessed. A careful cardiovascular examination should be performed with attention to significant cardiac murmurs and their alteration with body position and various maneuvers, evidence of left ventricular enlargement, and delayed or diminished carotid upstrokes. The extremities should be examined for diminished or absent peripheral arterial pulsations and for bruits.

A meticulous neurological examination with attention to the presence of nystagmus, anisocoria, facial asymmetry, plegia, ataxia, and dysmetria should be performed in all patients with syncope. Neurological findings that are focal, especially if recent in onset, suggest central nervous system pathology.

Electrocardiogram

The ECG is most commonly normal following a syncopal episode. Definitive diagnoses on initial ECG include marked sinus bradycardia, Mobitz II second- or third-degree atrioventricular (AV) block, alternating left and right bundle branch block, ventricular tachycardia (VT), pacemaker malfunction, paroxysmal supraventricular tachycardia (PSVT), sinus bradycardia, sinoatrial block, or pauses, if associated with symptoms. Such findings are rare (<5%) because arrhythmias resulting in syncope are often self-limited. Other electrocardiographic rhythm and conduction abnormalities can guide further evaluation. For example, first-degree or Mobitz type I second-degree AV block, sinus node dysfunction (SND), and bundle branch and fascicular blocks may suggest a bradycardic event, while evidence of prior myocardial infarction (MI) or left ventricular hypertrophy raises the possibility of VT.

RESULTS OF THE INITIAL EVALUATION

The simple initial evaluation described above is very effective in identifying patients at risk for a cardiovascular etiology for syncope (and therefore increased mortality). A large, prospectively followed cohort of emergency department patients presenting with syncope demonstrated that the four factors independently predicting increased risk of death in the following year are age greater than 45 years, history of congestive heart failure, history of ventricular arrhythmias, and abnormal electrocardiogram (not including sinus bradycardia, sinus tachycardia and nonspecific ST segment or T-wave abnormalities) at presentation (33). In patients with none of these four risk factors, mortality at one year was 1%, while it was 9%, 16%, and 27% for subjects with one, two, three, or more risk factors, respectively. Unfortunately, because age greater than 45 years is a risk factor, this
method is unable to identify any low risk older individuals. Another method for predicting risk in patients with syncope, the San Francisco Syncope Rule (34–37) relies on five risk factors: systolic blood pressure less than 90 mmHg, shortness of breath, non-sinus rhythm or new changes on electrocardiogram, history of congestive heart failure, or hematocrit less than 30%. Only one of 371 patients (0.3%) with no risk factors had a serious event within 30 days, whereas 52 of 342 patients (15.2%) with one or more of these risk factors had a serious event within 30 days.

In another investigation, only four of 146 patients not suspected to have structural heart disease following history, physical examination, and ECG were found to have had cardiovascular syncope after extensive evaluation (31). Patients with evidence of structural heart disease by history, physical examination, or ECG or those identified as high risk by the aforementioned risk scores should be admitted to the hospital for further evaluation. Diagnostic testing in this group should be aimed at defining the type of underlying heart disease as well as identifying whether a spontaneous arrhythmia is the cause of syncope. Among subjects with syncope and without structural heart disease, long-term follow-up is associated with an excellent outcome and relatively low (~15%) recurrence rate (38), obviating the need for inpatient evaluation.

THE ROLE OF ECHOCARDIOGRAPHY IN INITIAL EVALUATION

An echocardiogram may be beneficial in confirming or excluding structural heart disease, but may not be required in all patients. Echocardiography can directly diagnose a variety of dramatic cardiovascular conditions including severe valvular abnormalities, ventricular hypertrophy with outflow obstruction, severe pulmonary hypertension, and atrial myxoma or thrombus, but such findings are rare in the absence of a suggestive initial evaluation. In one study of 650 consecutive syncope patients (average age 60 years, with 44% > 75 years), echocardiography was useful mainly in confirming suspected severe aortic stenosis (AS) and in risk-stratifying patients with known cardiac disease by ejection fraction (EF). Echocardiography was normal or nonrelevanted in all patients without cardiac disease by history, physical, or ECG in this study group (39). The role of routine echocardiography in the evaluation of all patients with possible syncope remains to be fully defined, but data suggest that echocardiography is most useful for assessing the severity of the underlying cardiac disease and for risk stratification in patients with unexplained syncope who also have a positive cardiac history or an abnormal ECG (39). Accordingly, it seems reasonable to defer echocardiography in patients without suggestion of structural heart disease from history, physical examination, or ECG.

ETIOLOGICAL CATEGORIES AND DIAGNOSTIC TESTING

The remainder of this chapter will focus on the separate etiological categories of syncope as described above. A general description and salient pathophysiological information will be presented for each, followed by an examination of specific testing strategies and their efficacy. The frequency of use of typical diagnostic tests at our medical center and the estimated diagnostic efficacy of each from the literature are detailed in Table 4. These data highlight the discrepancy between the tests that are likely to yield definitive diagnoses, based on the published literature (40), and the current practice patterns that largely focus on low-yield nonprovocative testing.
Most of the etiologies in this category (such as subclavian steal syndrome, pulmonary embolism, and aortic dissection) can be directly diagnosed or at least strongly suggested by the initial clinical evaluation. A careful history and physical examination can guide specific confirmatory testing such as echocardiography, ventilation-perfusion or CT imaging, and angiography. Many of these conditions are relatively uncommon causes of syncope; the full diagnostic workup of these disorders is beyond the scope of this chapter and will not be discussed further here. The most common etiology in this category among the elderly is AS, myocardial ischemia resulting in cardiac pump failure, or arrhythmia, which is a rare primary cause of isolated syncope.

### AORTIC STENOSIS

Calcific or degenerative AS is the most common valvular lesion in the elderly. Risk factors include advancing age, congenital bicuspid valve, smoking, and hypertension; the estimated prevalence of critical AS approaches 6% by 86 years of age (41). Syncope occurs in up to 42% of patients with severe valvular AS, commonly with exercise (42). When patients with AS experience syncope not linked to exertion, the symptom may be unrelated to the valve disease (43). Dehydration or the use of vasodilating drugs may predispose individuals with AS to a decreased cardiac output and syncope. In patients with AS, syncope has prognostic significance with an average survival of two to three years in affected patients after its onset, in the absence of valve replacement. Physical findings in severe AS may include decreased amplitude and rate of the carotid pulse, paradoxical splitting of S2, and a very late-peaking systolic murmur heard best at
the right upper sternal border (occasionally at the apex in the elderly), as well as manifestations of pulmonary hypertension and congestive heart failure, if present (44). The diagnosis of critical AS is usually suggested by history and physical examination and may be confirmed with transthoracic echocardiography or left-sided cardiac catheterization.

**MYOCARDIAL ISCHEMIA**

Although one report suggests that syncope as a presenting manifestation of MI may increase in incidence with age, particularly in the oldest old (>80 years) (45), in a large observational series of hospitalized syncope patients (average age 73 years, with prevalence of known coronary artery disease 34%), syncope was caused by myocardial ischemia in only 1% (11). In another group of elderly patients, 77% had serial measurement of cardiac enzymes following admission for syncope; only one of 80 patients “ruled in” for MI, and this patient presented with unstable angina and syncope in the setting of chest pain (46). Although most patients admitted for syncope via the emergency department do not have an MI, serial cardiac enzymes are often obtained; in one series in 62% of subjects (47). However, only 2.1% (95% CI: 0.04–6.09%) had positive cardiac enzymes were obtained during their hospitalization in this study. Of the three patients with positive enzymes, two had chest discomfort and ST segment and T-wave abnormalities on ECG, and the third patient had dementia and could not recall the details surrounding her syncopal event, but had a left bundle branch block on baseline ECG. These data suggest that cardiac enzymes may be of little value when obtained routinely on elderly patients with syncope in the absence of signs or symptoms suggestive of myocardial ischemia. We would suggest that the diagnostic utility of “ruling out” active ischemia with serial cardiac enzyme testing in all elderly patients admitted with syncope is low in the absence of new ECG changes, symptoms of myocardial ischemia, or a history of ischemic events.

Cardiac stress testing in syncope has not been prospectively studied, but is unlikely to add to the diagnostic evaluation unless patients present with anginal features or exertional syncope. Even among patients who have syncope during exertion, severe AS, hypertrophic obstructive cardiomyopathy, pulmonary hypertension, or a vasodepressor response to exercise are probably more common (causes) than myocardial ischemia.

**PRIMARY ARRHYTHMIC SYNCOPE**

**Tachyarrhythmias**

Ventricular tachyarrhythmias are a relatively infrequent, but life-threatening etiology of syncope in the elderly. The increased prevalence of hypertension, diabetes mellitus, hypercholesterolemia, and coronary artery disease in the elderly increases the likelihood of associated left ventricular dysfunction from MI or cardiomyopathy in this cohort. Elderly patients also more commonly have left ventricular hypertrophy and AS, two conditions that predispose to ventricular dysrhythmias. The presence of a cardiomyopathy, ischemic or nonischemic in etiology, in the setting of syncope is a critical finding associated with a high rate of malignant events and outcomes, which may justify consideration of automatic implantable cardioverter defibrillator (AICD) implantation even if a malignant arrhythmia is never documented (48). The use of QT-interval-prolonging
medication or drugs that predisposes to hypokalemia or hypomagnesemia places elderly patients at risk for torsades de pointes.

Supraventricular tachyarrhythmias are a rare cause of syncope, but may be more likely to result in cerebral hypoperfusion in elderly patients with dehydration, on venodilating agents, or with diastolic dysfunction, where reliance on cardiac preload is high. These arrhythmias should always be correlated with symptoms prior to assuming that they are the cause of syncope.

Bradyarrhythmias

Bradyarrhythmias are a much more common etiology of syncope in the elderly than in the young. While bradycardia has traditionally been grouped with ventricular tachyarrhythmias and structural cardiovascular disorders under the heading of “cardiovascular syncope” in epidemiological studies, the excess mortality in patients with bradycardia is likely small in comparison. Bradyarrhythmias may result from intrinsic disease of the cardiac conduction system and/or extrinsic factors such as medications or autonomic influences.

Intrinsic conduction system disease may lead to (Sinus node dysfunction) SND and AV nodal block. SND has several presentations including sinus bradycardia, sinus pauses, and tachy-brady syndromes. Common tachy-brady syndromes include (1) PSVTs alternating with sinus bradycardia, (2) PSVTs followed immediately by pauses due to delayed sinus node recovery, and (3) persistent atrial fibrillation with slow or highly variable rates (indicating AV nodal block rather than SND). Interestingly, in patients with post-tachycardia pauses, syncope is likely to be because of the transient pause rather than the more obvious tachycardia.

Risk factors for the development of SND include age, structural heart disease (including infiltrative cardiomyopathies), and cardiac surgery. Symptomatic SND is an indication for permanent cardiac pacing (49), but survival in the elderly is related to the underlying structural cardiac disease and not to the presence of SND itself (50). High-grade AV block is another common cause of syncope in the elderly and indication for pacemaker placement (34) in the absence of contributing medications. Mortality in the oldest old (>80 years of age) is increased regardless of the presence of structural heart disease; in those aged between 65 and 79 years the picture is less clear, but syncope has been identified as an independent contributor to mortality (36).

Extrinsic causes of bradycardia include various medications and metabolic disorders, including hyperkalemia, acidosis, hypothyroidism, and hypothermia. Generally, these factors must be corrected before determining whether permanent pacing is indicated, unless bradycardic medication is required for concurrent tachyarrhythmias (tachy-brady syndrome). In elderly patients, bradycardic medications, including β blockers and rate-lowering calcium blockers, must be dosed cautiously and these two classes generally should not be used in combination. To avoid digoxin toxicity, current practice involves relatively low maintenance doses, which must be further adjusted according to the estimated glomerular filtration rate and drug interactions, notably with amiodarone. Reflex bradycardia is mediated by alterations in autonomic tone and is seen in neurally mediated syncope such as carotid sinus hypersensitivity (CSH) and the common “vasovagal faint.” In patients with reflex bradycardia, it is important to identify those with a significant vasodepressor component of a neurally mediated syndrome (see below), who may not derive much clinical benefit from standard pacemaker placement.

General indications for permanent pacing include (1) symptomatic bradycardia, (2) advanced conduction disease with a high risk of progression to symptomatic bradycardia, and (3) need for medical therapy that risks provoking symptomatic bradycardia.
(49) Elderly patients often resist pacer implantation because they are fearful, or they did not think they wanted such aggressive care. These concerns can be addressed by explaining the relative ease of the procedure, recovery, and aftercare. Also, device replicas are available so patients can see how small and unobtrusive they are. Ambulatory patients who still request conservative treatment of serious bradycardias may finally consent after considering the facial trauma and other injuries that can result from unexpected nonfatal syncope. The do-not-resuscitate (DNR) status is not an absolute contraindication to pacing, but the surgeon and anesthesiologist may request temporary suspension of DNR, so that they may treat unlikely procedural complications like ventricular arrhythmias or cardiac perforation.

**SHORT-TERM ECG MONITORING**

Short-term continuous ECG monitoring, such as telemetry or Holter monitor, is often utilized in an attempt to diagnose syncope etiology. However, patients with arrhythmia-related syncope may go weeks, months, or even years between recurrent events. Another central problem in attributing syncope to arrhythmias is that the vast majority of detected arrhythmias in patients with syncope are brief and result in no symptoms (51). Particularly in the case of bradycardia, abnormal rhythms on monitoring should be correlated with episodes of pre-syncope or syncope prior to initiating pacemaker therapy.

In one recent series of 649 syncope inpatients, telemetry monitoring was used in 100% of admissions. Abnormalities were found in only 7% of patients, with only 1% being diagnostic of syncope etiology (52). The duration of telemetry monitoring in hospital for an older individual with syncope has not been well studied, but data suggests that 24-hour monitoring may be insufficient (53) whereas durations longer than 48 hours are rarely necessary (54).

Outpatient Holter monitoring is similarly ineffective, with an incidence of symptom-correlated arrhythmias of approximately 4% in selected patients and less in unselected subjects (55). Thus, the efficacy of short-term ECG monitoring in diagnosing or ruling out arrhythmic causes of syncope is questionable, although the presence of frequent ventricular ectopy or nonsustained VT can be used to identify patients at higher risk for malignant arrhythmias and guide further testing (56).

**LONG-TERM ECG MONITORING**

In patients with multiple episodes of syncope separated by relatively long time intervals, longer-term ECG monitoring is useful. Patient-activated intermittent loop recorders may capture the rhythm during syncope after the patient has regained consciousness, since several minutes of retrograde ECG recording can be obtained. External event monitors are superior to Holter monitoring in the capture of arrhythmias during syncope and in suggesting alternate diagnoses when symptoms occur in the absence of any documented arrhythmia (57,58). Compliance with external event monitors for longer than one month is problematic, however, as patients must wear fixed electrodes during the entire monitoring interval. Additionally, as event monitors record only a five-minute interval of data, elderly patients or their caregivers must be able to activate recording shortly after an event.

The implantable loop recorder (ILR), which is placed in a subcutaneous pouch using local anesthesia (similar to a pacemaker) and has a battery life of 18 to 24 months, has increased the diagnostic yield of patients with unexplained syncope. In one series of
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64 patients, syncope was correlated with ECG evidence of arrhythmia in 27% of them (59). An excellent diagnostic yield has been suggested even in patients with recurrent syncope of unknown etiology after extensive testing. A small study of patients with negative workup including ambulatory ECG, TTT, and EPS demonstrated that 46% had symptom-correlated arrhythmias captured by ILR during a two-year follow-up period; most of these events were bradycardic in origin. Only 14% of patients had recurrence of symptoms during the first month, illustrating the limitation of external monitoring (60).

More recent data demonstrate that among patients referred for investigation of unexplained syncope, older adults (e.g., >65 years old) were more likely to have an indication for ILR implantation than those younger than 65 years; ILR also had a higher diagnostic value, with an arrhythmia being more likely to be detected and successfully treated (61). Up-front costs of implantation are high, and the procedure carries a small risk of local complications. However, cost-benefit analyses suggest that the increased diagnostic yield from ILR in the long run may lead to decreased overall expenditure in syncope diagnosis (62). A recent randomized assessment of ILR versus a “conventional” diagnostic strategy, including EPS and TTT, in elderly patients with syncope showed significantly improved (52% vs. 20%) diagnostic accuracy in the ILR group. However, patients with left ventricular EF less than 35% and patients with clinical symptoms suggesting neurally mediated syncope were excluded from the study group, biasing the results in favor of ILR (63). While the optimal duration of monitoring with ILR is unknown, a 12-month monitoring period is associated with identification of 90% of episodes, suggesting that this is a reasonable duration (64).

ELECTROPHYSIOLOGICAL STUDY

After the routine assessment of syncope has failed to yield a diagnosis or establish a treatment plan, EPS may have one of the highest yields among available supplemental testing strategies in appropriately selected patient populations. One study of 75 elderly patients with recurrent syncope referred for EPS found that 68% had abnormalities that could have produced syncope, including SND (55%); abnormal His bundle conduction (39%); and inducible VT (14%) (65). Despite this potential, EPS was performed in only 2% of 1516 elderly adults hospitalized for syncope in one observational study (11).

EPS involves the placement of several catheters into the right atrium and ventricle of the heart via central venous cannulation. Intracardiac electrograms can be obtained and electrical stimuli can be delivered through the catheters to precipitate and record arrhythmic events. However, patients with critical AS, severe hypertrophic obstructive cardiomyopathy, unstable angina, decompensated heart failure, or uncorrected left main or severe three-vessel coronary artery disease should be excluded from EPS. An EPS carries the standard risks of infection and bleeding from any invasive procedure; more serious complications, such as pulmonary embolus, pneumothorax, and cardiac perforation leading to pericardial tamponade, are rare, but more likely in the elderly.

A diagnostic study is defined by the following: (1) inducible sustained monomorphic VT; (2) PSVT with symptomatic hypotension; (3) significant delay in His-Purkinje conduction; and/or (4) SND as delineated by sinus node recovery time greater than three seconds. Induced atrial fibrillation, SVT without hypotension, polymorphic or nonsustained VT, and ventricular fibrillation (VF) are generally regarded as nonspecific findings. Even “diagnostic” findings on EPS must be interpreted with
caution, as concerns exist regarding the sensitivity, specificity, and clinical consequences of a positive study. Routine evaluation with EPS in patients with suspected bradycardia is not recommended because of its low sensitivity.

The advent of effective therapy for malignant ventricular tachyarrhythmias via the AICD has profoundly changed the importance of risk stratification for life-threatening VT. Any discussion of EPS to diagnose VT-induced syncope is by nature tied to this life-saving therapy. Several trials have shown a decrease in overall mortality following AICD implantation in survivors of cardiac arrest with severely decreased left ventricular EF (66–68). The data supporting the use of EPS for the diagnosis of VT in syncope comes from the observation of high-risk patients following AICD implantation. In a trial of 178 patients with syncope and inducible monomorphic VT on EPS and 568 patients with documented clinical sustained VT or VF who were followed prospectively after AICD implantation, the actuarial probability of appropriate AICD therapy in both groups was 49% at one year, and clinical outcomes did not differ. Recurrent syncope in this trial was associated with VT or VF in 85% to 90% of episodes (69). Little data exist, but AICDs capable of antitachycardia pacing and earlier termination of VT events may lead to fewer episodes of syncope in these patients (70). However, the efficacy of AICDs in persons aged 75 years and older presenting with syncope is not clear.

The diagnostic yield of EPS in patients with unexplained syncope is much greater in those with preexisting heart disease (71) [i.e., those with a previous MI, EF < 0.40, and/or an abnormal rest ECG (especially, bundle branch block)] (72). Such patients should be strongly considered for EPS following even their first episode of syncope, unless an alternative diagnosis is clear from initial evaluation or the patient’s overall clinical state, or if long-term prognosis is poor.

Electrophysiological testing is unlikely to demonstrate a potential cause of syncope in patients who have no structural heart disease, a left ventricular EF greater than 0.40, no ventricular ectopic activity during cardiac monitoring, and a normal ECG. Such a clinical profile in a patient with multiple syncopal episodes predicts with a high degree of certainty (>99%) that the EPS will be negative and the risk of sudden death low (53). It should also be noted that while syncope in patients with nonischemic dilated cardiomyopathy is a predictor of sudden death (73), the sensitivity and specificity of EPS in this population are insufficient to make it useful in the prediction of ventricular tachyarrhythmias (74,75). Therefore, after other causes of syncope have been ruled out, patients with nonischemic dilated cardiomyopathy and a suspected arrhythmic event may qualify for ICD implantation even without EPS.

EPS has a much higher predictive value in patients with ischemic heart disease compared to those without ischemia. Patients with prior MI or ischemic cardiomyopathy who have unexplained syncope may be referred for EPS, usually after active ischemia has been ruled out or corrected. Patients with ischemic heart disease and a negative EPS have an excellent long-term prognosis with respect to mortality. In two trials of patients with nondiagnostic or negative EPS after syncope, the incidence of sudden death was 2% after follow-up of two to three years. Syncope recurrence in these patients, however, was still common at approximately 20%. Most of these episodes were found to be noncardiac in origin; those with cardiovascular etiologies were most often found to have bradycardia missed by EPS (76,77).

While EPS may be a high-yield diagnostic test in the elderly patient with structural heart disease and syncope, the decision to undergo EPS should be made on a case-by-case basis. Patients with poor functional capacity, severe cognitive impairment, or comorbidities likely to result in death within a relatively short period of time are probably not appropriate candidates. Likewise, patients who do not want definitive therapy such as permanent
pacemaker or AICD implantation may have an unacceptable risk–benefit ratio with EPS as well. Furthermore, in patients who already have received an AICD for primary or secondary prevention, the device does not prevent progression of the underlying heart disease. As the end of life approaches, palliative options, including device inactivation, should be discussed to avoid repeated, ineffective shocks for terminal arrhythmias.

NONINVASIVE ASSESSMENT OF RISK FOR VT

Noninvasive strategies for the prediction of ventricular tachyarrhythmias are attractive in the elderly population, particularly in patients reluctant to undergo EPS. Two techniques currently in use are the signal-averaged ECG (SAECG) and T-wave alternans (TWA) testing. However, data supporting the efficacy of either test in the evaluation of syncope are limited, and these tools cannot be applied to a significant portion of elderly patients with other than normal sinus rhythm.

The SAECG averages multiple QRS complexes in the attempt to identify “late potentials,” delayed electrical conduction through diseased areas of the myocardium. It is more difficult to interpret in patients with bundle branch block or intraventricular conduction delay, as the lengthened overall depolarization time obscures the low-amplitude late potentials. This test has not been studied prospectively in outcomes related to syncope, but has been evaluated with respect to predicting the results of EPS. In patients with unexplained syncope, the combination of prior MI and abnormal SAECG had a positive predictive value of 60% for inducible VT at EPS, but the real utility of a SAECG may be to exclude patients at high risk for VT (77).

The TWA analyzes microvolt changes in the T-wave (repolarization) portion of the ECG on an every-other-beat basis, and is usually performed during exercise to increase sensitivity. The test cannot be interpreted in atrial fibrillation or with frequent premature cardiac beats. Patients with microvolt T-wave alternans, particularly in the setting of prior MI or dilated cardiomyopathy, show a higher incidence of ventricular arrhythmias. A large prospective trial of patients undergoing EPS (41% with syncope) have suggested that the relative risk of malignant ventricular arrhythmia (average follow-up 297 days) in patients with positive TWA was 10.9 as compared with 7.1 for inducible VT on EPS and 4.5 for SAECG (78). However, no trials using TWA specifically to examine patients with syncope have been published. Furthermore, many elderly patients may be unable to exercise to a sufficient heart rate, and pharmacologically assisted TWA testing has not been well studied to date. Thus, the use of TWA for risk stratifying elderly individuals with syncope is not recommended at present.

OH AND DYSAUTONOMIC DISORDERS OF BLOOD PRESSURE CONTROL

OH is an important cause of syncope in the elderly. Following the assumption of a standing position, gravity induces pooling of blood in the lower extremities. Blood pressure is normally maintained in this setting of decreased circulatory volume by vasoconstriction and increased heart rate. Numerous age-related changes in cardiovascular structure and function, including impaired baroreflex function, diastolic dysfunction, a higher prevalence of disorders that directly or indirectly impair autonomic function, the common use of vasoactive medications, and impairment in salt and water balance, all contribute to an increase in the incidence and prevalence of OH in the elderly.
All elderly patients with syncope should have measurement of orthostatic vital signs. Which parameter (systolic, diastolic, or mean blood pressure) is the best measure of orthostasis, how long patients should stand before blood pressure is measured, and what defines a significant change in blood pressure have not been well studied. The most commonly accepted definition is a decline of greater than 20 mmHg in systolic blood pressure or greater than 10 mmHg in diastolic blood pressure on standing. In the vast majority of patients with OH, the drop in blood pressure is detected within two minutes of assuming upright posture (79). However, in certain patients, there is a delayed orthostatic intolerance and blood pressure progressively falls over 15 to 45 minutes. This response, which can be detected during TTT, is termed a dysautonomic response to upright posture.

OH is a common finding in the elderly and is frequently not associated with symptoms (80). In one prospective study of 223 patients with syncope, OH was detected in 69 patients (31%), but was common in patients for whom other probable causes of syncope were assigned following evaluation (61). Syncope should not be attributed to orthostatic changes alone unless orthostatic symptoms are present or systolic blood pressure declines to less than 90 mmHg on postural change (81).

Decreased intravascular volume and adverse effects of drugs are the most common causes of symptomatic OH in the elderly (62). The status of the patient’s hydration preceding the syncopal event should be assessed along with the daily intake of salt and alcohol. The medications most commonly contributing to orthostasis in the elderly are nitrates, diuretics, antihypertensives, anti-Parkinsonian drugs, antidepressants, and antipsychotics. Potent vasodilators must be titrated very cautiously in this population. Certain situational factors may predispose elderly patients to orthostasis, notably the redistribution of circulatory volume to the splanchnic circulation following a meal. An evaluation of 47 community-dwelling elders and three patients admitted for syncope evaluation indicated that symptomatic hypotension during TTT occurred earlier and increased in incidence from 12% to 22% in the postprandial state (82).

OH may also be an important manifestation of autonomic dysfunction resulting from a wide variety of diseases and drugs. The Shy–Drager syndrome is associated with autonomic failure and involvement of the corticospinal, extrapyramidal, and cerebellar tracts, including a Parkinson-like syndrome. Parkinson’s disease itself can be associated with autonomic dysfunction. Lesions of the spinal cord caused by cervical trauma and other disorders, such as transverse myelitis, syringomyelia, and various tumors, may result in severe OH. OH may also be a manifestation of peripheral neuropathy that involves sympathetic fibers. This may be associated with such diseases as diabetes mellitus, amyloidosis, porphyria, chronic alcoholism, and pernicious anemia.

TREATMENT OF OH AND DYSAUTONOMIAS

Treatment for OH and dysautonomias includes mechanical interventions (e.g., compressive devices such as stockings or abdominal bands, counterpressure maneuvers like squatting or leg crossing); pharmacological interventions including both the withdrawal of potentially exacerbating medications (e.g., diuretics, vasodilators); and institution of pharmacological therapy [salt (NaCl) pills, mineralocorticoids, midodrine, and possibly pyridostigmine]. The management initially consists of education, advice, and training on various factors that influence blood pressure. Increased water and salt ingestion effectively improves orthostatic blood pressure. Subsequent treatment options discussed below include physiological interventions such as leg crossing, squatting, elastic abdominal binders, and stockings. Among the available pharmacological therapies,
salt pills and the mineralocorticoid fludrocortisone are often employed initially; second-line therapy may include sympathomimetics such as midodrine. In older individuals, supine hypertension may coexist with OH and may be exacerbated by treatment of the latter condition. Some degree of supine hypertension may have to be tolerated to minimize the short-term risk of orthostasis and associated falls. Additionally, pyridostigmine may be a useful agent in such patients. Mineralocorticoids also may cause hypokalemia.

In elderly individuals with syncope, review of medications with special attention to agents that can cause or contribute to dehydration and vasodilation are essential first steps in the treatment algorithm for OH and dysautonomias. Indeed, following the adage that “less is more,” clinicians should first consider which pharmacological agents could be discontinued or reduced in dosage prior to adding pharmacological therapy. While salt and fludrocortisones have been initial therapy for patients with disordered blood pressure regulation, they have not been subjects to rigorous controlled trials and carry the risk of exacerbating hypertension and other states common in older individuals associated with abnormal volume regulation, including renal insufficiency, cirrhosis, and heart failure.

Compressive devices for the lower limbs (e.g., compression stockings, bandage wrap, and others) are an effective non-pharmacological therapy especially for older individuals with OH (83). Recent randomized data have demonstrated that elastic compression stockings of the legs and abdomen are associated with the amelioration of declines in tilt induced blood pressure, with improvement in symptoms (90% asymptomatic in the active therapy versus 53% in the control arm), and with improvements in symptoms over the first month (84). Another study demonstrated similar efficacy using abdominal compression alone, which increases standing blood pressure to a varying degree by increasing stroke volume (85). Compression of all compartments is the most efficacious, followed by abdominal compression, whereas leg compression alone has been shown in a small study to be less effective (86), presumably reflecting the large venous capacity of the abdomen relative to the legs. We have found that older individuals have difficulty applying commonly available over-the-counter compressive stockings secondary to arthritic limitations and concomitant peripheral vascular disease and often express concern about the inability to regulate the degree of compression applied by such devices. Accordingly, the use of elastic bandages, which are available in a roll (e.g., ACE bandages) may facilitate application and provide the ability to self-regulate how tightly such devices are applied.

Squatting, bending forward, and leg crossing can improve orthostatic blood pressure in patients with OH, primarily by augmenting venous return, thereby increasing cardiac output. Studies suggest that targeting the splanchnic circulation has the greatest effect on orthostatic blood pressure changes (87), again presumably because of the larger capacitance of the splanchnic versus limb beds. Suitability and effectiveness of a specific counter maneuver depend on the orthopedic or neurological limitations of each older individual with syncope and probably should be individually evaluated for efficacy before recommending long-term adherence.

The α-adrenergic agonist, midodrine, is approved by the Food and Drug Administration for the treatment of OH. In a multicenter, randomized, placebo-controlled study, 10-mg dose of midodrine or placebo three times per day for six weeks improved standing systolic blood pressure and symptoms, independent of the severity of OH, use of fludrocortisone, or compression garments. The main adverse effects were those of pilomotor reactions, urinary retention, and supine hypertension. Cautious administration of midodrine to older individuals who are at risk of supine hypertension with dosing early in the morning and early afternoon, when orthostatic symptoms are at their worst, is
advised. This schedule permits two to three hours of upright activity after each dose. Patients must be instructed to avoid lying down after drug treatment with midodrine and to rest in a seated, rather than supine, position if they grow tired during the day. Symptoms of OH tend to lessen during the evening, and it is recommended to avoid pressor agents at that time of day. Rarely, midodrine induced supine hypertension has been suggested to cause or contribute to severe cerebrovascular complications.

Acetylcholinesterase inhibition with pyridostigmine has emerged as a potentially novel treatment for patients with both OH and supine hypertension (88). There have been several small trials among approximately 100 individuals. Trials in patients with neurogenic OH found statistically significant improvement in standing diastolic blood pressures (89–91). In one study, a single 60-mg dose of pyridostigmine bromide compared with placebo, with or without midodrine, did not affect supine blood pressure but did prevent the decline in diastolic blood pressure (91). However, long-term data has shown significant rates of discontinuation (92). At this time, further data are needed prior to supporting a definitive role for pyridostigmine in patients with OH and supine hypertension.

NEURALLY MEDIATED DISORDERS OF BLOOD PRESSURE CONTROL

This collection of disorders involves a neural reflex mediated by the nucleus tractus solitarius, an area in the brain stem that regulates blood pressure. The receptors for the afferent limb of the reflex are contained in several possible locations; examples include the left ventricle (vasovagal syncope), carotid sinus body (CSH), pharynx, or trachea (cough syncope), and the bladder (post-micturition syncope). In susceptible individuals, stimulation of the reflex results in withdrawal of sympathetic vasomotor tone and vasodilatation with resultant syncope. When accompanied by bradycardia, the term “vasovagal” is used, while the term “vasodepressor” is employed for reflex reactions that are not accompanied by significant bradycardia.

Vasovagal Syncope

The “simple faint” has traditionally been considered a disease of the young patient. Early studies of elderly institutionalized and community-dwelling patients indicated that syncope was neurally mediated in only 1% to 5% of cases (1,6). At the time, neurally mediated syncope was diagnosed with the classical features of a precipitating event followed by nausea, pallor, and sweating. The elderly more commonly have syncope without a prodrome, or with retrograde amnesia for the event, making diagnosis by history alone problematic. More recently, use of TTT has suggested that neurally mediated syncope is much more common in the elderly than previously believed, and likely constitutes a significant fraction of those previously carrying an “unknown” diagnosis.

Carotid Sinus Hypersensitivity

CSH may be a relatively underappreciated cause of unexplained falls and syncope in the elderly, with a prevalence in elderly adults presenting to the emergency department with unexplained falls of 34% in one trial (93). However, a significant percentage (39%) of older adults without syncope meet criteria for CSH (94), indicating that the finding of a hypersensitive response should not necessarily preclude further investigation for other causes of syncope (95). Attacks may be precipitated by factors that exert pressure on the
carotid sinus (tight collars, shaving, sudden head turning), a history of which is obtained in one-quarter of patients with this syndrome. Syncope from CSH occurs predominantly in men, 70% of whom are older than 50 years; the majority of patients have coronary artery disease or hypertension. Other predisposing factors include cervical pathology such as enlarged lymph nodes, scars resulting from neck surgery; carotid body tumors, and parotid, thyroid, or head and neck tumors.

CSH can produce bradycardia and/or vasodilatation, and is classified according to its predominant hemodynamic manifestation. Cardioinhibitory CSH is defined as sinus pauses greater than three seconds, while vasodepressor CSH is denoted as a fall in systolic blood pressure greater than 50 mmHg; if both mechanisms are noted, then the disorder is termed mixed-type CSH. The diagnosis is made with CSM, which some investigators consider positive only if symptoms are also reproduced during the examination (96).

**TILT TABLE TESTING**

In TTT, patients are secured to a motorized table with a footboard, and brought quickly to an upright position at an angle of 60° to 80° while undergoing ECG and beat-to-beat blood pressure monitoring. Various protocols have been evaluated for the provocation of neurally mediated syncope through TTT, either in the drug-free state or with various pharmacological agents (nitroglycerin, isoproterenol, and adenosine). In general, sensitivity of TTT increases with the use of pharmacological agents, longer duration of TTT, and a greater angle of head uptilt. However, with the addition of pharmacological agents, the specificity declines (97,98).

In patients with negative EPS, rates of hypotension on upright TTT (without pharmacological provocation) of 27% to 67% are reported as compared to approximately 10% in controls without syncope (99–102). A retrospective evaluation of TTT in 352 subjects with unexplained syncope (including 133 patients >65 years and 43 patients >80 years) showed an age-related decline in positive responses. However, a surprisingly high proportion of elderly patients with unexplained syncope had a positive TTT (37% of patients aged ≥65 years, and 23% of patients aged ≥80 years). Notably in this study and another (103), the hemodynamic response in those subjects with neurally mediated syncope differed by the age of the subjects. In younger patients, a cardioinhibitory response is more often demonstrated (e.g., vasovagal response), while in the elderly, a vasodepressor response is more common. These data demonstrate that a large proportion of elderly patients may have neurally mediated syncope that may be difficult to diagnose based on clinical grounds alone (104). Upright TTT can confirm the diagnosis in these patients and can help reassure patients that they have an excellent long-term prognosis with regard to mortality.

**CAROTID SINUS MASSAGE**

Many physicians have been hesitant to perform CSM because of the theoretical risk of stroke. However, after excluding patients with clinical history of stroke, or transient ischemic attack, and/or audible carotid artery bruits, the risk of neurological complications was 0.17% to 0.45% in two studies on the safety of the maneuver (66,105). Patients with history of VF or VT should be excluded, as ventricular dysrhythmias during CSM have been reported, albeit rarely, in this setting. CSM should
be performed on one side at a time by applying gentle digital pressure for five to 10 seconds at the bifurcation of the carotid artery, below the angle of the jaw at the level of the cricothyroid cartilage. The procedure was initially performed only in the supine position, but CSM in the upright position (usually performed during a TTT session) increases sensitivity (106). The distinction between cardioinhibitory and vasodepressor types is important, so the test should be performed with continuous beat-to-beat blood pressure monitoring in addition to continuous ECG if possible. Dual-chamber pacing has been shown to prevent falls in patients with cardioinhibitory CSH (67), but the benefits in mixed-type and vasodepressor forms of CSH are less clear.

TREATMENT OF NEUROLY MEDiated SYNCOPE

Treatment of neurally mediated reflex syncope consists of the following: (1) reassurance regarding the benign nature of the problem, (2) education about avoidance of predisposing factors and triggering events, (3) recognition of preceding symptoms and maneuvers to abort the episode, and (4) avoidance of volume depletion and prolonged upright posture. Salt supplements and water intake are often part of this initial approach. When these initial efforts are ineffectual and a more aggressive treatment strategy is needed, pharmacological and pacing therapies can be employed. While a review of each therapy is beyond the scope of this chapter, several points are worth noting.

In older individuals, because of concerns for treatment related side effects, especially in frail older adults, and because of the lack of definitive controlled data in this population, physiological interventions (e.g., compressive devices such as stockings or abdominal bands, counterpressure maneuvers including squatting, leg crossing, and isometric hand grip) are preferred initial strategies, while pharmacological interventions (β blockers, salt pills, fludrocortisone, midodrine) and electrical therapies should be reserved for more severe cases. Among the multitude of drugs that have been used for the treatment of neurally mediated syncope, uncontrolled or short-term controlled trials have shown satisfactory or favorable results that unfortunately have not been confirmed in the majority of long-term, placebo-controlled, prospective trials. These trials also have generally failed to randomize a representative population of older individuals (107).

β Blockers are often considered as the first-line drugs, traditionally used to treat neurally mediated syncope, in part because tilt table–induced faints generally are preceded by increased blood levels of catecholamines (108). β Blockers, due to their negative inotropic effect, have been proposed to lessen the degree of ventricular mechanoreceptor activation associated with an abrupt decrease in venous return and to block the effects of elevated circulating adrenaline, but this theory has not been supported by randomized controlled trials. In fact, several studies raise questions about their routine use. A case control study of patients with neurally mediated syncope demonstrated that recurrent syncope was actually more frequent in those receiving β blockers (109). Atenolol 50 mg/day has been shown to be ineffective in preventing syncopal recurrences in a double-blind, randomized clinical trial (110); there was a trend toward a better outcome in patients treated with placebo, and adverse events occurred more frequently in the active arm of this study. Additionally, the multicenter Prevention of Syncope Trial (POST), a randomized, placebo-controlled, double-blind trial designed to assess the effects of metoprolol in vasovagal syncope over a one-year treatment period demonstrated that metoprolol was not effective in preventing vasovagal syncope in the study.
population (111). Accordingly, we have stopped employing β blockers as initial therapy for neurally mediated syncope.

While α agonists have a clear and well-defined role in treating patients with OH and dysautonomias (see Treatment of OH above), their role in patients with neurally mediated syncope is less clear. Etilerine, an α agonist, was not effective in preventing syncopal recurrences in a large, multicenter, double-blind study [Vasovagal Syncope International Study (VASIS)] (112). Midodrine, another α agonist, has been shown to be effective in reducing symptoms and improving quality of life in the short term in patients with very frequent “hypotensive” symptoms (e.g., >1 syncope/month) (113,114). However, the data supporting the use of midodrine in neurally mediated syncope are far less compelling than those presently available for OH.

The role of pacemakers in managing patients with neurally mediated syncope characterized by prolonged (e.g., >3 seconds) sinus pauses is not clear. Four randomized clinical trials of pacing therapy have been conducted to date; three of these were positive (115–117), while the only one that was blinded was negative (118). When the 289 patients from all four studies are analyzed collectively, syncope recurred in 18% (25/140) of the paced patients and in 45% (67/149) of nonpaced patients. Ongoing randomized studies such as International Study on Syncope of Uncertain Etiology (ISSUE-3) (119) will further clarify the role of pacemakers in this syndrome. At present, pacing therapy appears effective in some, but certainly not in all patients with neurally mediated syncope. Pacing is only effective for neurally mediated syncope associated with asystole and has no role in treating the vasodilation that is frequently the dominant hemodynamic event in neurally mediated syncope. At present, cardiac pacing probably should be reserved for after other therapies have failed and only as a last resort in a highly selected small subgroup of patients affected by severe and recurrent neurally mediated syncope.

For patients with carotid sinus syndrome (CSH and symptoms), cardiac pacing may be beneficial, with its efficacy demonstrated by two randomized, controlled trials (93,120). However, neither of these trials was blinded, and thus the true treatment effect of pacing for patients with CSH remains unknown. Interestingly, in patients with abnormal asystolic responses induced by CSM, spontaneous asystolic episodes during long-term follow-up occurred in 74% of subjects, with asystolic episodes of greater than 3 seconds and greater than 6 seconds after 2 years of follow-up occurring in 82% and 53%, respectively (121). Accordingly, an asystolic response to carotid sinus stimulation may predict the occurrence of spontaneous asystolic episodes during follow-up and thus could be useful in identifying elderly subjects in whom pacing therapy would be ultimately beneficial.

PRIMARY NEUROLOGICAL SYNCOPE

As previously noted, primary neurological causes of syncope are relatively rare. Despite this finding, examination of current clinical practice indicates that specific neurological testing is performed in approximately half of syncope evaluations (Table 1) (12,41).

SEIZURES AND ELECTROENCEPHALOGRAPHY

In patients with a clinical history compatible with a seizure or suggestive findings such as tongue biting, electroencephalography (EEG) may be beneficial in confirming the diagnosis. However, EEG should not be performed routinely in the evaluation of patients
with syncope. In one study of the 99 patients referred for EEG because of syncope, near-syncope, or related complaints, 15 had abnormal findings, but in only one patient was the final diagnosis or treatment of the syncope affected by the EEG. In addition, almost all patients with abnormal EEG had clinical histories compatible with seizures or focal neurological findings on examination (122). Since cerebral hypoperfusion can provoke a seizure (convulsive syncope), the presence of a seizure should not exclude primary syncope as the underlying event.

STROKES, TRANSIENT ISCHEMIC ATTACKS, AND SPECIFIC TESTING

In the elderly, cerebrovascular atherosclerosis and impaired cerebrovascular autoregulation secondary to hypertension can contribute to cerebral hypoperfusion in a variety of circumstances. However, syncope is generally not a primary manifestation of cerebrovascular disease unless disease of the posterior circulation is present. When secondary to vertebrobasilar disease, syncope is almost always accompanied by other neurological symptoms traced to ischemia in the same territory, such as vertigo and ataxia (123,124). The common practice of cerebrovascular imaging via ultrasonography or other methods has not been extensively studied in this setting, but in the absence of suggestive history, probably contributes little to diagnosis (125).

Brain imaging in the evaluation of syncope yields helpful information only in the setting of a suggestive history or abnormal findings on neurological examination. A review of 195 patients estimated the diagnostic yield of head CT at 4%; in all of these patients, a witnessed seizure or focal neurological examination was present (17). In the setting of syncope and suspected head trauma, CT scanning may be indicated to exclude a subdural hematoma.

SUGGESTED DIAGNOSTIC ALGORITHM

Determining the underlying cause and risk stratification for subjects with syncope relies on the performance of a complete history, physical examination (including orthostatic vital signs), and ECG. Approximately one-third of patients have a clear diagnosis evident at presentation. Another third of patients have a particular etiology highly suggested after initial evaluation, and directed testing can be performed in this group to confirm the suspected diagnoses. Since primary neurological causes of syncope are unlikely, specific neurological tests are rarely useful in the absence of a suggestive history and physical examination. A suggested strategy for the diagnosis of syncope in the elderly patient is detailed below and in Figure 2 (126). However, strict adherence to a guideline is contrary to the basic principles of geriatric medicine and geriatric cardiology, in which heterogeneity and complexity are the norm rather than the exception. Accordingly, it behooves every practitioner to place this strategy in the context of the individual patient and modify it according to individual nuances and personal preferences.

In the remaining patients with unexplained syncope after initial evaluation, cardiac testing, specifically with consideration of methods to evaluate for malignant tachyarrhythmias, should be performed in patients with structural heart disease. For patients with recurrent unexplained syncope without structural heart or cardiac conduction system disease (or patients with structural heart disease and negative cardiac testing), TTT to evaluate for OH and neurally mediated causes is appropriate. This test should be performed
prior to long-term ECG monitoring to identify the significant percentage of subjects with neurally mediated syncope and resultant bradycardia who do not require pacing. If the etiology of syncope is still undetermined following directed cardiac and autonomic testing, long-term ECG monitoring should be employed. The ILR has excellent potential to obtain a diagnosis in these patients even if external monitoring is negative, particularly if episodes are separated by long time intervals.

CONCLUSIONS

Syncope is common in the elderly and is associated with significant morbidity and mortality. It is a symptom, not a disease, and has a complex differential diagnosis ranging from benign to malignant causes; elderly patients commonly have multiple possible contributing factors. The assignment of the underlying etiology can be greatly facilitated through an understanding of syncope epidemiology and the utility of relevant diagnostic tests. Identifying patients with underlying structural heart disease is important for risk stratification. In the elderly, multiple origins of syncope frequently coexist and need to be addressed. Particular emphasis should be given to the impact of polypharmacy, orthostatic intolerance, postprandial hypotension, and CSH (127). For patients with unexplained syncope, provocative tests (EPS, TTT, and CSM) are more likely to yield a definitive diagnosis than observational testing strategies. Table 5 summarizes the treatment options for different causes of syncope.
ACKNOWLEDGMENTS

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REFERENCES


Table 5  Syncope Treatment Options

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<td>Correct reversible causes</td>
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<td>Pacing</td>
<td>Anti-arrhythmic drugs</td>
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| Structural cardiac disease                        |
| Medical therapy                                   |
| Coronary revascularization                        |
| Aortic valve surgery and valvuloplasty           |

| Orthostatic hypotension                           |
| Compressive devices                               |
| Salt and fluids                                   |
| Mineralocorticoids                                |
| Midodrine                                         |

| Neurogenic syncope                                |
| Avoid precipitants                                |
| Options for OH as above                          |
| Consider pacing for reflex bradycardia            |

Abbreviations: ICD, implantable cardioverter defibrillator; OH, orthostatic hypotension.
Evaluation of Syncope in the Elderly Patient


Evaluation of Syncope in the Elderly Patient


Anticoagulation in the Elderly

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CARDIOVASCULAR INDICATIONS FOR ANTICOAGULATION

Anticoagulants have been a part of the medical armamentarium for more than 50 years. These drugs inhibit thrombosis, which is the incipient event in many cardiovascular diseases such as myocardial infarction, stroke, and peripheral arterial disease. Thrombus embolization from the atria can occur in association with atrial fibrillation (AF), from the ventricles in congestive heart failure and cardiomyopathy, from the valve surfaces in valvular heart disease, and from the diseased vessels in peripheral arterial disease, causing stroke and/or gangrenous limbs. Similarly, venous thrombosis and embolization also produces significant cardiovascular disease, peripheral venous disease, and pulmonary emboli. The clinical indications for the use of anticoagulants in each of these disease states, described in detail in prior chapters, are summarized below. This chapter will discuss the different therapeutic options, the pharmacologic basis for these therapies, and the management of therapy in different cohorts of patients.

Atrial Fibrillation

AF is a common condition in the elderly, affecting almost 10% of those older than 80 years (1). In those with AF, the incidence of thromboembolic stroke in untreated patients is 4.5% per year. This risk is further increased by several risk factors: (i) a history of ischemic stroke or cerebrovascular accident, transient ischemic attack (TIA), or systemic embolism; (ii) age more than 75 years, (iii) moderately or severely impaired left ventricular function, and/or congestive heart failure; (iv) a history of hypertension; or (v) diabetes mellitus. Pooled data from clinical trials undertaken during the 1980s have demonstrated that warfarin provides a 68% relative risk reduction for stroke in patients with AF (2), and is superior to aspirin (3). The American College of Chest
Physicians (ACCP) has issued guidelines for anticoagulation for patients in the following categories (1):

1. Persistent or paroxysmal AF or atrial flutter with risk factors for stroke (as listed above): anticoagulation with a vitamin K antagonist (VKA) such as warfarin, with a target international normalized ratio (INR) of 2.5, range 2–3.

2. AF of more than 48 hours or unknown duration, and anticipated cardioversion (electrical or chemical): anticoagulation with a VKA, target INR of 2.5, range 2–3. Anticoagulation should be administered for three weeks prior to the procedure, and for four weeks afterward. Alternatively, anticoagulation with warfarin or heparin can be administered for five days, at which time a transesophageal echocardiogram is performed to determine if a left atrial thrombus is present. If a thrombus is not present, cardioversion can proceed, followed by four weeks of anticoagulation. If a thrombus is present, then anticoagulation should be continued indefinitely.

Occasionally, a surgical procedure, known as the Maze procedure, is performed for AF (4). Multiple incisions are made in the atrium to disrupt reentrant circuits. These incisions are then sewn together, leaving one path for nerve propagation. This procedure is quite effective in restoring sinus rhythm. Patients undergoing the Maze procedure, without other indications for anticoagulation, require only short-term anticoagulation with a VKA, typically three months and with a target INR of 2.5, and then are placed on low-dose aspirin. Prior stroke or TIA, if thought secondary to AF, is not an indication for long-term therapy.

Valvular Heart Disease and Prosthetic Heart Valves

Valvular heart disease is also associated with systemic embolism and thromboembolic stroke due to formation of thrombi associated with the abnormal or diseased valve, either native or prosthetic. The ACCP recommends that the following groups of patients with valvular heart disease be treated with anticoagulants (5):

1. Mitral valvular disease (native): warfarin, target INR of 2.5 (range 2–3)
   - patients with rheumatic mitral valve disease and any of the following: AF, history of systemic embolism, left atrial diameter of greater than 5.5 cm; indefinite therapy;
   - patients undergoing mitral valvuloplasty, for three weeks before and four weeks after the procedure;
   - patients with mitral annular calcification complicated by systemic embolism, indefinitely.

2. Mechanical prosthetic heart valves: indefinite therapy with VKAs, “bridging” therapy with heparin until a VKA is therapeutic, is required.
   - aortic valves: all valves except caged ball or caged disk valves: indefinite therapy with VKA, target INR of 2.5 (range 2–3);
   - mitral valves: all valves except caged ball or caged disk valves: indefinite therapy with VKA, target INR of 3 (range 2.5–3.5);
   - mechanical valves and additional risk for thromboembolism (AF, myocardial infarction, left atrial enlargement, endocardial damage, low ejection fraction): indefinite therapy with VKA, target INR of 3 (range 2.5–3.5) with low dose aspirin, indefinitely;
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3. Caged ball or caged disk valves: INR of 3 (range, 2.5–3.5) in combination with low-dose aspirin.

3. Bioprosthetic valves—mitral and aortic: For the first three months, patients should be given a VKA, target INR of 2.5 (range 2–3), with “bridging therapy” until the INR is therapeutic. If AF is not present, low-dose aspirin may be used after this initial period. If there is a history of systemic embolism or AF, then 12 months to indefinite treatment with anticoagulation with a target INR of 2.5 (range 2–3) is recommended.

Ischemic Heart Disease

The pathophysiology underlying acute and chronic coronary artery disease (CAD) is that of atherosclerotic plaque rupture and thrombosis within the arterial system. The formation of a platelet plug is an early event in the sequence of events, thus antiplatelet agents, such as aspirin and clopidogrel, play a critical role in therapy. Anticoagulant agents, however, also have an important role in the treatment and interventional management of CAD. The ACCP guideline for anticoagulant use in CAD (6) is summarized below:

1. Acute management of non-ST-elevation acute coronary syndromes: low-molecular-weight heparins (LMWH) are preferred, or alternatively, weight-adjusted unfractionated heparin (UH) administered to an intensity, as measured by the activated partial thromboplastin time (aPTT), of 50 to 75 seconds over control, is recommended in addition to antiplatelet therapy for short-term management, and continuing the therapy, if percutaneous coronary intervention is undertaken. The ACCP recommends against the use of direct thrombin inhibitors in this clinical situation.

2. Post–myocardial infarction and post–acute coronary syndromes: aspirin is the preferred therapy. Aspirin alone is preferred over aspirin plus warfarin, except in those individuals who are at high risk for thromboembolism defined as those with a large anterior myocardial infarction, systolic hypertension, a left ventricular thrombus identified on echocardiogram, or a history of thromboembolism.

3. Primary prevention of CAD: aspirin or warfarin (INR target of 2.5, range 2–3) is recommended for the primary prevention of CAD.

Peripheral Arterial Disease

The pathophysiology of peripheral arterial disease is analogous to that of CAD, except that it occurs in larger arterial systems supplying the extremities. Therefore, for patients with chronic limb ischemia, antiplatelet therapy is the mainstay of management and anticoagulants are not recommended. Anticoagulants have a role in the management of patients with acute limb ischemia. The ACCP (7) recommends UH therapy followed by long-term warfarin therapy for acute limb ischemia (arterial thrombosis and/or embolism).

Venous Thromboembolic Disease

Anticoagulant agents are the mainstay of primary and secondary prevention of venous thromboembolic disease, which includes both deep venous thrombosis (DVT) and pulmonary embolism (PE). Elderly patients present a higher risk for thrombosis and
embolization with venous thromboembolic disease than do younger patients given the same clinical circumstances (8). Patients considered at high risk are those in whom one or more of Virchow’s triad is present—venous stasis, tissue injury, and hypercoagulability. Examples of clinical situations in which stasis occurs are hospitalized patients who are confined to bed, patients with lower extremity hemiparesis, or congestive heart failure. Tissue injury is a common occurrence in most surgical procedures; for example, Hypercoagulability is associated with infection, cancer, hormone therapy, and the nephrotic syndrome (9,10).

In elderly patients, in whom anticoagulants are administered for prophylaxis of venous thromboembolic disease, adherence to dosage recommendations made by the manufacturer is important. Adjustments for renal function should be considered when anticoagulant therapy is initiated, and reconsidered during periods of clinical instability when renal function may deteriorate. Consideration of the duration of therapy must also be done initially and during the course of therapy, depending on clinical circumstances. Finally, special deliberation must be applied to the use of anticoagulant prophylaxis for patients who are to undergo neuroaxial analgesia or anesthesia. The ACCP recommendations for prophylaxis of venous thromboembolic disease (11) applicable to the elderly are as follows:

1. General recommendations:
   - Mechanical methods of thromboprophylaxis, graduated compression stockings (GCS), or intermittent pneumatic compression (IPC), should be used primarily in patients who are at high risk of bleeding, or in addition to anticoagulant-based prophylaxis.
   - The ACCP recommends against the use of aspirin for venous thromboembolic events (VTE) prophylaxis.
   - Consider dosing guidelines suggested by the manufacturer.
   - Renal impairment should be considered when dosing LMWHs, fondaparinux, the direct thrombin inhibitors, and other drugs renally cleared, particularly in the elderly who are at high risk of bleeding.
   - Special caution should be employed when using anticoagulant prophylaxis in patients undergoing neuroaxial anesthesia or analgesia.

2. General surgery, major gynecological surgery, and major open urologic surgery: all elderly patients by virtue of age are considered “high risk.”
   - Thromboprophylaxis should be treated with low-dose UH (LDUH) 5000 U q8h, or intermediate dose LMWH daily. For cancer surgery, higher doses of LMWH are usually recommended, and posthospital discharge prophylaxis with LMWH can be considered in selected patients.
   - For those high-risk general surgery patients with multiple risk factors, anticoagulant thromboprophylaxis should be combined with GCS or IPC.

3. Vascular surgery: anticoagulant prophylaxis is not routinely recommended unless additional risk factors are present. If so, then LDUH or LMWH are recommended.

4. Orthopedic surgery:
   - Elective total hip replacement (THR): one of the following three anticoagulant regimens is recommended: (i) LMWH at the usual high-risk dose, begun 12 hours before surgery or 12 to 24 hours after surgery, or four to six hours after surgery at half the usual high-risk dose the following day; (ii) fondaparinux, 2.5 mg started six to eight hours after surgery; or (iii) adjusted-dose VKA started preoperatively or the evening after surgery (target INR of 2.5, range 2–3).
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- Total knee arthroplasty (TKA): LMWH, fondaparinux or adjusted-dose VKA (target INR of 2.5, range 2–3), or the optimal use of IPC are recommended.
- Hip fracture surgery (HFS): LMWH, fondaparinux, or adjusted-dose warfarin (target INR of 2.5, range 2–3) are recommended.
- THR, TKA, or HFS: patients receive thromboprophylaxis for at least 10 days, and for those undergoing THR or HFS, prophylaxis should be extended for up to 28 to 35 days postoperatively.
- Arthroscopic surgery: the ACCP does not recommend anticoagulation for patients who are not at high risk for thrombosis.
- Laparoscopic surgery: the ACCP recommends against routine thromboprophylaxis other than aggressive mobilization.
- Medical inpatients and intensive care unit patients should undergo risk assessment for venous thromboembolic disease risk. Prophylaxis should be provided with LDUH or LMWH for the vast majority of elderly patients admitted to the hospital who are immobilized or have increased risk for hypercoagulability.

The anticoagulant agents used in the treatment of venous thromboembolic disease in elderly patients are analogous to that in other populations. The ACCP provides guidelines (12) for treatment of venous thromboembolism to prevent recurrence. Recent data regarding the management of idiopathic venous thrombosis suggest that these patients have a propensity for clotting and have a high rate of recurrence with discontinuation of anticoagulation, necessitating consideration of indefinite or lifelong therapy. This assessment for an elderly patient may be somewhat different from that in a younger patient, given that their history of thrombosis is known. If this is negligible, the motivation to continue therapy beyond the standard interval may be somewhat less for a younger patient in whom the duration of prior observation is less. In addition, the risk for bleeding in an older adult may be greater. Nevertheless, the ACCP recommendations do not differ according to age, and the clinician must make decisions regarding treatment duration on the basis of individual assessments of the potential risk and benefit for a patient. The ACCP guidelines (12) are summarized below:

1. Initial treatment of acute venous thrombosis: LMWH or dose-adjusted UH [intravenous (IV) or subcutaneous (SC)] along with initiation of a VKA (warfarin) on the first day. Heparin may be discontinued after five days if a stable INR of 2 or greater has been achieved.
2. Long-term treatment of acute venous thrombosis of the leg: for patients with an inciting event or a reversible risk factor for VTE, treatment should be of at least three months duration. For those with idiopathic DVT, treatment should continue for at least 6 to 12 months, with consideration of indefinite therapy. For patients with cancer, LMWH is recommended for three to six months of therapy or for the duration of the cancer.

PATHOPHYSIOLOGY OF THROMBOSIS

Fibrin Clot Formation and the Coagulation Pathways

Arterial thrombosis, and perhaps embolization, is the initiating event for many cardiovascular diseases. Hemostasis is the process by which a fibrin clot is formed at a site of endovascular injury. The formation of a fibrin clot (and its dissolution) is carefully regulated through a cascade of events. It begins with the mechanical or spontaneous
rupture of an atherosclerotic plaque, thereby exposing its lipid core, which is thrombogenic. Platelets adhere, activate, and aggregate, forming a platelet plug. Clot formation is further propagated by activation of the coagulation cascade. Venous clots occur in low flow sites and are largely comprised of fibrin and red cells, in contrast to the platelet core of arterial clots, which occur in high-pressure arterial sites.

The clotting cascade involves precursor proteins or proenzymes called the coagulation factors. Most of these proteins are synthesized in the liver (except von Willebrand factor) and may undergo post-translational modification. The γ-carboxylation of glutamic acid residues of the vitamin K–dependent factors II (prothrombin), VII, IX, and X, required for their procoagulant activity, is one example of posttranslational modification. Some anticoagulants interfere with the production and function of coagulation factors, such as the VKAs, and act at various points in the coagulation cascade to disrupt thrombosis.

Clotting is initiated by the generation or exposure of tissue factors at a site of injury. This activates the clotting “cascade,” where the precursor proteins (proenzymes) are cleaved by proteases to become activated enzymes themselves. Classically this sequence has been divided into the “intrinsic” and “extrinsic” coagulation cascade, although this may not be the actual sequence of events in vivo (Fig. 1). Both the extrinsic and intrinsic cascades result in a final common pathway in which factor Xa mediates the conversion of prothrombin to thrombin (factor IIa). Factor Xa catalyzes the formation of fibrin from fibrinogen as well as activating other clotting factors through feedback mechanisms. Fibrin reinforces the platelet plug.

The formation of just the right amount of clot is due to the interaction between thrombosis and fibrinolysis. As the fibrin clot develops, lysis of the clot closely follows. When clotting is unmodulated, it leads to thrombosis, vascular inflammation, and tissue damage, as seen in DVT, myocardial infarction, and stroke. Modulation of clotting is achieved through the removal of activated clotting factors by the reticuloendothelial system (predominantly in the liver), dilutional effects, antithrombotic pathways through enzymes such as antithrombin III, the protein C pathway, and fibrinolysis. Other mechanisms have an impact on vascular and platelet function.

Figure 1  The coagulation cascade and sites of anticoagulant action.
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The intrinsic and extrinsic clotting pathways provide a framework for assessing the activity of the coagulation factors in the laboratory. The intrinsic pathway is initiated by exposure of clotting factors to a negatively charged surface, measured in vitro by exposure to silica in the aPTT test. Thromboplastin, a tissue-like factor, is used in the prothrombin clotting time (PT) test to measure the activity of the extrinsic pathway proteins. The activity of thromboplastins varies across laboratories, as quantified by their international sensitivity index (ISI). The INR is a standardized method of monitoring the extrinsic pathway proteins and is calculated from the PT, which has been calibrated for the ISI of the thromboplastin used. It is the test used for monitoring of the VKA warfarin.

Thrombosis and Aging

The incidence of both venous and arterial thromboses increases significantly with age (13). The etiology is uncertain, but it is likely to be multifactorial. In addition to the increase in risk factors for atherosclerosis, an increase in coagulation factors, with their ability to serve as substrates and enzymes in the clotting reactions (particularly factors VIII, IX, and fibrinogen) without a “compensatory” increase in anticoagulant factors, has been observed with aging (14). In addition, increased platelet activity, changes in vessel walls, and increases in indicators of inflammation associated with aging (interleukin-6 and C-reactive protein) (15,16) may also produce a prothrombotic state. Acquired factors such as the increased incidence of hospitalizations, cancer, immobility, and age-related increases in body mass index also play a role. A large community-based study from France (17) found the annual incidence of symptomatic VTE to be 1.83 per 1000 (1.24 for DVT and 0.60 for PE). The combined incidence rose with age, regardless of gender, to 10 per 1000 in those older than 75 years. Another study of male inpatients with a DVT or PE at 16 short-stay hospitals (8) identified an annual incidence of DVT by age of 24 per 1000 for those aged 40 to 49 years, 43 per 1000 for those aged 50 to 59 years, 144 per 1000 for those aged 60 to 69 years, and 265 per 1000 for those aged 70 to 79 years. The exponential increase in the incidence of PE, with or without DVT, was also similar for both genders.

Despite the observed increase in coagulation factors with aging, thrombosis often does not occur. The advocates of this theory ascribe the aging-associated heightened incidence of thrombosis to associated comorbid conditions and the increase in these markers to a survival bias or a protective effect of inhibiting tumor angiogenesis (14).

ANTICOAGULANT AGENTS

Anticoagulant agents currently employed in clinical practice act via several mechanisms: (i) indirect anticoagulants, which work through a plasma cofactor antithrombin III (ATIII) such as heparin, LMWH, and pentasaccharides; (ii) VKAs, principally warfarin in the United States; and (iii) direct thrombin inhibitors.

Heparins, LMWHs, and Pentasaccharides

Heparin is a naturally occurring material in animal tissue, which is comprised of a mixture of long chains of branched glycosaminoglycans. Naturally occurring UH is a heterogeneous mix of glycosaminoglycans with a molecular weight of 5000 to 30,000 daltons (10,18), with a mean molecular weight of 300 Da/saccharide unit. There are, on average, 40 saccharide units in UH. A specific five-sugar (pentasaccharide) sequence of heparin
binds to ATIII, a plasma cofactor, greatly enhancing the activity of ATIII. The heparins are indirect thrombin inhibitors since they are all dependent on this ATIII interaction. The resultant heparin-ATIII complex binds and inhibits serine protease–coagulation factors, particularly thrombin (IIa) and Xa. The different heparins inhibit the different coagulation factors to differing extents. UH-ATIII complexes will inhibit thrombin and Xa in equal amounts. To inhibit thrombin, the heparin must be able to span the thrombin-ATIII complex; this requires approximately 18 saccharide units or a molecular weight of 5400. In contrast, the ability of the heparin-ATIII complex to inhibit Xa is not dependent on chain length.

LMWHs—enoxaparin, dalteparin, and tinzaparin—are derived from heparin through enzymatic or chemical degradation of the chains. Typically, they have a mean molecular weight of 5000 Da and a mean of 17 saccharide components, approximately 20% of which include the pentasaccharide portion responsible for ATIII binding. Since the mean molecular weight of LMWH is 5000, and the average number of saccharide units is 17, this shorter number of saccharide units binds thrombin less efficiently. Therefore, the LMWH-ATIII complex has less of an inhibitory effect on thrombin and acts principally against factor Xa in a 3:1 or 4:1 ratio.

The key pentasaccharide sequence found in UH and LMWH has been synthesized to produce a long-acting and potent pentasaccharide, marketed in the United States as fondaparinux. Given the decreased thrombin binding efficiency with the smaller number of saccharide units, it is not surprising that fondaparinux is too small to have any binding to thrombin; its anticoagulant action is directly and purely against Xa.

Interestingly, as the number of saccharide units decrease and the heparin is less able to bind to thrombin, the better the heparin is at releasing tissue factor pathway inhibitor (TFPI). However, this does not appear at this stage to play a significant role in anticoagulation therapy.

Unfractionated Heparin

Pharmacology. Only about a third of the dose of UH binds to ATIII and produces an anticoagulant effect. The other chains are inactive, binding to other plasma proteins, endothelial cells, and platelet factor 4 (PF4). Clearance of heparin is inversely related to the chain length. As a result of the heterogeneity of chains in UH, the nonspecific binding to plasma proteins and cells, as well as its clearance, is variable. This lack of pharmacokinetic predictability is mirrored in its variability in anticoagulant effect and mandates the need for close monitoring.

UH is administered by SC injection or intravenously. Its half-life is approximately one hour following an IV bolus, and longer with SC administration. Because of a reduction in bioavailability with SC administration, it is recommended that the SC dosages be increased by 10% over the IV dosage (19). UH is metabolized by the liver and is renally excreted. It does not require a dosage adjustment for renal dysfunction, which is common in the elderly.

Initial dosing. UH can be prescribed for the prophylaxis or treatment of arterial and venous thromboses. For prophylaxis against VTE in medical, orthopedic, and surgical patients, it is usually dosed as 5000 U subcutaneously every eight hours (11).

The dosing of intravenously administered UH is ultimately based upon results from monitoring. Initial dosing is estimated on the basis of weight (18,20). For treatment of venous thromboembolism, an initial bolus of 80 U/kg is administered, followed by an
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18 U/kg/hr infusion. Initial dosing for acute coronary syndromes is usually somewhat lower, 60 to 70 U/kg (maximum dose 5000 U), followed by an infusion of 12 to 15 U/kg/hr (maximum dose, 1000 U/hr) to achieve an aPTT of 50 to 75 seconds (21–23). For patients undergoing percutaneous coronary interventions, heparin is often administered along with glycoprotein IIb/IIIa inhibitors, which may increase the risk of bleeding, and sometimes requiring the dose to be reduced. The efficacy of fixed-dose weight-adjusted SC dosing of UH for acute treatment of venous thromboembolism has also been demonstrated, and can be initiated as a bolus dose of 333 U/kg, followed by subsequent doses of 250 U/kg (24,25).

Monitoring. As has been described, the anticoagulant effect of heparin is unpredictable due to the number and length of the glycosaminoglycan chains. Following initial dosing, the anticoagulant effect is monitored to achieve and maintain a therapeutic level. Monitoring is most commonly accomplished in the United States with use of the aPTT test, with a recommended therapeutic range of 1.5 to 2.5 times the control result. This is based upon a historic study that demonstrated that this intensity of anticoagulation reduced the risk for recurrent thromboembolism (26). The aPTT is usually obtained six hours after the bolus and infusion is initiated, and the heparin infusion is adjusted accordingly, often through the use of nomograms like the Raschke nomogram by Raschke (18,20). Although the therapeutic range at any institution should be established by correlation of the aPTT with anti-factor Xa levels, any individual’s aPTT is the composite result of all the coagulation factors involved in the aPTT sequence. Thus, a patient with a high factor VIII level or an increased fibrinogen can have a lower aPTT, despite adequate anti-Xa levels. In addition, increases in the aPTT can occur with coincident use of warfarin, thrombolytics, as well as in the presence of antiphospholipid antibody and clotting factor deficiencies (27).

It is critical for both efficacy and safety that therapeutic levels be achieved quickly. When IV UH is used in the treatment of acute venous thromboembolism, the risk of recurrence is greatly increased for those patients who have not achieved a therapeutic aPTT level within 24 hours (28,29).

Adverse effects. Thrombocytopenia and bleeding are the two most important adverse effects of UH during short-term usage. Heparin also increases vessel wall permeability, inhibits vascular smooth muscle cell proliferation, suppresses osteoblast formation, and activates osteoclasts. As a result, heparin is associated with bone loss, which may become clinically relevant in elderly patients with a longer duration of use.

Platelet monitoring and heparin-induced thrombocytopenia. UH can cause thrombocytopenia through two mechanisms: a nonimmune form of thrombocytopenia, called “heparin-associated thrombocytopenia,” or “type I heparin-induced thrombocytopenia.” “Type II heparin-induced thrombocytopenia,” often called “HIT,” is an immune syndrome associated with antibody formation. Although less common, HIT is associated with much more significant morbidity as arterial and venous thromboses can be associated.

Type I heparin-associated thrombocytopenia occurs in 10% to 20% of patients (30,31). It is not a progressive thrombocytopenia, is usually mild in nature with platelet counts greater than 100 × 10^9/L, and, as a result, is not usually associated with bleeding. This type of heparin-associated thrombocytopenia is usually managed conservatively by discontinuation of heparin and monitoring of the platelet count, which usually rises to pretreatment levels within several days (30).
HIT is suspected in patients in whom the platelet count falls by greater than 50% within 5 to 14 days of initiating UH, or in those patients presenting with thromboses who have recently been treated with heparin. Platelet counts may fall precipitously in those who have been recently treated with heparin and have residual antibodies. IgG-antibody formation to platelets begins with formation of an antibody directed against the complex of heparin and PF4. While the Fab portion (of the antibody) is directed against the heparin-PF4 component, the Fc portion of the antibody binds to the Fc, RIIa receptors on platelets, and potentially to Fc receptors on leukocytes, and to the endothelium (32). It is thought that these antibodies and the resultant activation of platelets cause further injury and release tissue factor microparticles that induce thrombosis (33).

The diagnosis of HIT requires both clinical and serological findings; the finding of antiplatelet antibodies alone is not sufficient. Clinical criteria include a fall in platelet counts by greater than 50% or to less than $100 \times 10^9/L$, and a new thrombotic or thromboembolic event. Both arterial and venous events occur, but the majority events are venous, and include DVT, PE, and dural sinus thrombosis. Arterial thromboses occur in 25% of patients, which include aortic occlusion, myocardial infarction, stroke, and peripheral thromboses (30).

Surgical patients are at highest risk for HIT, perhaps due to the prevalence of heparin use for thromboprophylaxis. In patients exposed to UH, about 1% to 3% develop HIT (31). It is more commonly associated with the use of bovine, rather than porcine UH, and has been identified in only 0% to 0.8% of patients treated with LMWHs (34). In the case of LMWH, it may be that prior exposure to UH is a prerequisite.

HIT is a common in-hospital problem and it is estimated that 25,000 to 50,000 people in the United States develop HIT annually (35). Venous thrombosis is associated with HIT, called HITT, in approximately one out of every eight patients (36) and some studies suggest that over 50% of patients with HITT will develop thrombosis within one month (37). Thus, anticoagulant therapy is required during the management of HIT and HITT for at least three months. Direct thrombin inhibitors such as argatroban or bivalirudin are usually used, as discussed subsequently.

Because of the prevalence of type I thrombocytopenia, and the morbidity of type II, the ACCP has recommended that platelet counts be monitored every other day until day 14, or until therapy is discontinued, for those receiving therapeutic doses of UH (31). For those restarting UH within 100 days of prior treatment, the ACCP recommends obtaining a platelet count prior to treatment and repeated after 24 hours. No monitoring is required for LMWH if UH use has not preceded it. Fondaparinux does not cause HIT, and a recent review of the literature supports the use of fondaparinux to treat HIT/HITT successfully (38).

Reversal of the anticoagulant effects. Reversal of the anticoagulant effects of heparin may be required when a procedure is planned or during an episode of significant bleeding, whether or not the dosage is therapeutic. Given the short half-life, the most common action is to discontinue the drug and, after four to six hours, test the aPTT to determine if normal clotting has been reinstated. If clinically significant bleeding is encountered, immediate reversal is required along with support of the patient, which may include transfusion, fluid support, and other interventions. Immediate reversal of the effect of heparin is achieved by IV protamine, a basic protein that binds to heparin to form a salt with a 1 mg protamine: 100 U heparin ratio. For an IV infusion of heparin, the infusion should be stopped and protamine given. For prior SC doses of heparin, an infusion of protamine may be required. Protamine must be infused slowly as it can be associated with severe adverse reactions such as hypotension or bradycardia (18).
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Low-Molecular-Weight Heparin

Pharmacology. The LMWHs currently in use in the United States include enoxaparin, dalteparin, and tinzaparin. These agents are derived from heparin by enzymatic or chemical degradation, but consist of smaller chains. This reduces the level of nonspecific binding, which, in turn, improves the predictability of their anticoagulant effect, which is mediated by binding the key pentasaccharide sequence to antithrombin III. The LMWHs are not interchangeable, and have different approved indications. The reduced molecular size of the LMWH molecules impedes their excretion, providing a longer half-life as compared with UH, which provides an advantage for dosing frequency. This may be a disadvantage, at times, for elderly patients who develop significant renal insufficiency.

Dosing and monitoring. LMWHs are administered subcutaneously in fixed or body-weight adjusted doses once or twice daily for prophylaxis or treatment. For patients with significant renal insufficiency, defined as a creatinine clearance of less than 30 mL/min, the use of some LMWHs for treatment of venous thromboembolic disease is either not recommended (39) or should be reduced in dosage (40). Some data on dalteparin suggests that, like tinzaparin, modification may not be necessary (41). Dosing of LMWHs is also somewhat unclear for obese patients weighing more than 150 kg, although the evidence suggests that the LMWH dosages are linear to 190 kg (39,42).

As discussed, UH has a 1:1 activity against factors Xa and IIa, whereas the LMWHs have between 2:1 and 4:1 anti-Xa:anti-IIa activity. This renders the aPTT test problematic for monitoring of LMWHs for general clinical use. Because of the greater predictability of LMWH bioavailability, monitoring of anticoagulation activity is not usually required. The anti-Xa assay may be used for monitoring under special circumstances such as with use in obese patients or those with renal insufficiency.

Adverse effects and reversal. The adverse effects of LMWHs are similar to, but less frequent than, those with heparin. HIT has been infrequently reported. The reduced incidence of HIT with LMWHs is thought to be due to reduced binding to PF4 on the endothelium and platelets, although this is uncertain. Bleeding is also somewhat less frequently reported with the use of LMWH as compared with UH. In a large meta-analysis of LMWHs versus UH treatment of acute DVT, LMWHs were associated with lower mortality rates over three to six months of patient follow-up, with lower rates of major bleeding, and at least comparable efficacy for the prevention of thromboembolic recurrences (43,44). Current guidelines from the American College of Physicians and the American Academy of Family Physicians have recommended the use of LMWH over UH (45).

LMWHs can be partially reversed (about 60% of anti-Xa activity) through the use of protamine. Supportive therapy, including fluids and transfusion, awaiting the clearance of LMWHs is also critical (18).

Pentasaccharides: Fondaparinux and Idraparinux

Pharmacology, dosing, and monitoring. Fondaparinux is a synthetic molecule containing only the key pentasaccharide sequence necessary for antithrombin binding found in heparin and LMWHs, and selectively inhibiting factor Xa (46). It has no effect on TFPI. It is virtually 100% bioavailable because of the lack of polysaccharide chains, it is specific for Xa, and it reaches peak plasma levels in two hours (46). Like the LMWHs, there is no correlation with aPTT levels. Monitoring is not necessary, but can be accomplished with anti-Xa levels.
Fondaparinux is administered subcutaneously. It has a 17-hour excretion half-life because of its small molecular size, allowing once daily dosing for treatment (7.5 mg) and prophylaxis (2.5 mg) (46). Dosing must be reduced for renal insufficiency. Fondaparinux should not be used for those patients with a creatinine clearance of less than 30 mL/min, which may pose some difficulty for elderly patients (47).

Idraparinux is a more sulphated derivative of fondaparinux, which binds much more avidly with antithrombin III, producing a 130-hour half-life. This allows weekly dosing for many individuals (48). It is undergoing clinical trials but is currently not available for use in the United States.

Adverse effects and reversal. Bleeding is the most common adverse effect of fondaparinux and has been reported to be comparable to that of LMWHs (49). Its long half-life and irreversibility pose significant challenges to its use in patients with a higher likelihood of bleeding. It has not been associated with the production of heparin-PF4 antibodies, and HIT and HITT have not been reported. Indeed, as suggested above, it has been used in the treatment of HIT/HITT.

VITAMIN K ANTAGONISTS

Bishydroxycoumarin or dicoumarol was discovered more than 50 years ago as the active agent in sweet clover, which was observed to cause cattle to die of hemorrhage. Warfarin was synthesized on the basis of the structure of dicoumarol. Warfarin today remains the most widely used anticoagulant agent in the United States, largely because of the ability to administer it orally. Although warfarin is prescribed for a wide variety of thrombotic and thromboembolic indications, it remains underutilized because of the large number and types of drug interactions associated with its use, difficulty in dosing, narrow therapeutic index, and need for close monitoring.

Warfarin

Pharmacology

Warfarin inhibits the interconversion of vitamin K and its 2,3 epoxide. This inhibits the vitamin K–induced γ-carboxylation of coagulation factors II (prothrombin), VII, IX, and X, although its antithrombotic effect is thought to be most dependent on the reduction of factors II and X. The endogenous anticoagulant proteins C, S, and Z are also vitamin K–dependent, enabling warfarin to have the potential to act as a procoagulant as well.

Warfarin exists as a racemic mixture of R and S enantiomers, with the S enantiomer having about two to five times greater intrinsic activity, although it is more rapidly cleared. Warfarin is readily absorbed with peak concentration within four hours, and approximately 99% is bound to plasma proteins. S-warfarin is metabolized stereoselectively by the hepatic microsomal enzymes cytochrome P450-2C9 (CYP2C9) with an effective half-life of 40 hours (50–52). The gene encoding the hepatic microsomal enzyme P450-2C9 has several less active variants identified among different ethnic groups. These mutations cause an increased sensitivity to warfarin and may be associated with an increase in adverse clinical outcomes in certain ethnic groups (53). Similarly, mutations in the vitamin K epoxide reductase (VKORC1) gene have been associated with variations in warfarin sensitivity.

Hepatic dysfunction can cause impaired synthesis of clotting factors as well as decreased metabolism of warfarin, and thus an increase in drug response (and an increase in INR). Renal function does not have an impact upon the response to warfarin. Warfarin
resistance is a very rare condition in which alteration of the receptor is present. Smoking can also cause a decreased response to warfarin, although the mechanism is unknown (54) and cholestatic disease can hinder the absorption of this fat-soluble vitamin K (55).

There is some evidence that there is decreased clearance of warfarin with age. In a study of dosage by age among 532 patients in an anticoagulation clinic, the average dose for patients younger than 75 years was 4.9 mg of warfarin to maintain the INR in the therapeutic range (INR, 2–3), whereas those aged 75 to 84 years required 4 mg, and those aged 85 years and older, required 3.5 mg (56). Other pharmacodynamic interactions include synergisms with other agents that also impair hemostasis such as the concurrent use of aspirin, or competitive antagonism due to dietary vitamin K, discussed below.

## Drug and Dietary Interactions

The dose-response to warfarin varies considerably between individuals because of genetic factors related to the gene encoding the microsomal enzyme P450-2C9, along with other factors such as decreased or increased dietary intake of vitamin K, liver disease, smoking, comorbid disease, and the use of other medications. Drug interactions occur through a variety of mechanisms. Rarely interactions occur through inhibition of warfarin absorption, such as can occur with use of cholestyramine. More commonly, medications may alter 2C9 induction (57), increasing warfarin clearance, and reducing antithrombotic activity (e.g., phenytoin, rifampin) (58). Some β-lactam antibiotics contain the side chain N-methyl-thio-tetrazole, which inhibits vitamin K-dependent carboxylation (59), but many antibiotics may affect the vitamin K2 production by intestinal flora.

Others interact through stereoselective pathways. Those that inhibit the metabolism of the S-enantiomer preferentially will have a greater impact on the INR than those interacting with the R-enantiomer; a drug such as amiodarone (60) has a very significant impact due to its interaction with both. Other drugs cause nonselective enzyme inhibition (e.g., sulfamethoxazole, metronidazole) (61), which increases the antithrombotic effect (and the INR). Although uncommon, yet other medications may displace warfarin from plasma proteins, increasing antithrombotic activity.

A detailed listing of prescription drug interactions with warfarin can be found in the drug labeling, other references, or through the use of computerized drug interaction programs. Data regarding interactions with herbal preparations are more difficult to obtain. It may be difficult, however, to estimate the timing and intensity of impact of a drug interaction on the INR in an older adult, who may be taking a number of medications concurrently. An increase in the frequency of monitoring is essential during periods of changes in medications.

Vitamin K is a fat-soluble vitamin usually derived from plant material that plays a critical role in the activity of warfarin. It is important to maintain a diet with a relatively constant level of vitamin K. Patient education is important to identify the foods which are rich in vitamin K as well as the dietary supplements such as Viactiv®, a popular calcium supplement, as well as Ensure® supplements. Grapefruit juice, however, does not appear to alter the anticoagulant response to warfarin (62). In addition, a variety of medications, foods, and disease can interfere with the absorption and intestinal synthesis of vitamin K by intestinal flora. Malnutrition and malabsorption can cause an increase in the response to warfarin because of a decline in vitamin K stores. Antibiotics alter vitamin K synthesis.

## Dosing

The anticoagulant and antithrombotic effect of warfarin requires several days of therapy to achieve because of the long half-life of some of the critical vitamin K-dependent clotting factors. Initial and chronic dosing of warfarin has undergone significant study. Larger
loading doses have not been proven to have any advantage in achieving a more timely sustainable therapeutic level. Although a more recent study found initiation with 5 mg and 10 mg to be equivalent (63), the 5-mg dose has been more consistently found to be superior to 10 mg (64,65), and is preferred for elderly patients who require a lower chronic dose of warfarin (56). Warfarin is usually initiated with 5 mg unless a drug, disease, or dietary interaction is anticipated. The maintenance dose estimated in initial dosing should also be lower. A nomogram developed by Crowther (66) uses an initial 5-mg dosage as depicted in Table 1.

Another study of elderly inpatients initiated anticoagulation with a standing dose of 4 mg daily for three days (67). On the fourth day, the dose was adjusted according to that day’s INR (target INR, 2–3) according to an algorithm (Table 1). The use of this algorithm predicted the maintenance dose well, with a low rate of over-anticoagulation.

Gage (68) has suggested another method for initial dosing of warfarin. For a patient with a baseline INR of 1, if the INR obtained 15 to 24 hours later after the initial dose is greater than 1.5, a very low daily dose of warfarin (e.g., 1 mg) will be required. If the INR is of 1.2 to 1.3, then the patient will require a low daily dose (2–3 mg) and a second dose of 5 mg should be given. If the INR remains 1.0 to 1.1 after a second dose of 5 mg, a higher dose (e.g., 7.5 mg) can be given.

Several nomograms (63–69) and computer software programs (70–72) are also available to assist with initial and subsequent dosing of warfarin. Although none of these have proven to be superior to manual dosing by experienced medical staff for lower INR ranges, they are superior for dosing at higher INR levels (73), since medical staff are often reluctant to raise doses to the necessary higher levels in the elderly.

Patients managed manually have dosages adjusted by estimation. One method commonly employed is to calculate the current weekly dose of warfarin, and adjust this dosage, eventually dividing it across seven days. It is thought that patient adherence is improved if the daily dose remains constant, rather than alternating, as patients may not

Table 1 Comparison of Two Algorithms for Initiating Warfarin Therapy

<table>
<thead>
<tr>
<th>Day of therapy</th>
<th>INR</th>
<th>Warfarin dose (mg)</th>
<th>INR</th>
<th>Warfarin dose (mg)</th>
</tr>
</thead>
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<tr>
<td></td>
<td></td>
<td>Crowther’s algorithm (66)a</td>
<td></td>
<td>Siguret’s algorithm (67)a</td>
</tr>
<tr>
<td>1</td>
<td>5</td>
<td></td>
<td></td>
<td>4</td>
</tr>
<tr>
<td>2</td>
<td>5</td>
<td></td>
<td></td>
<td>4</td>
</tr>
<tr>
<td>3</td>
<td>&lt;1.5</td>
<td>10</td>
<td>&lt;1.3</td>
<td>5</td>
</tr>
<tr>
<td>2.0–2.5</td>
<td>2.5</td>
<td>1.3–1.49</td>
<td>4</td>
<td>3</td>
</tr>
<tr>
<td>&gt;2.6</td>
<td>0</td>
<td>1.5–1.69</td>
<td>3</td>
<td>3</td>
</tr>
<tr>
<td>&lt;1.5</td>
<td>12.5</td>
<td></td>
<td></td>
<td>2</td>
</tr>
<tr>
<td>4</td>
<td>5–7.5</td>
<td>1.7–1.89</td>
<td>2</td>
<td>1</td>
</tr>
<tr>
<td>&gt;3.0</td>
<td>0</td>
<td>&gt;2.5</td>
<td>2</td>
<td>measure INR daily, omit doses until INR &lt;2.5, then 1 mg</td>
</tr>
<tr>
<td>5</td>
<td>&lt;1.5</td>
<td>12.5–15</td>
<td>&gt;2.5</td>
<td></td>
</tr>
<tr>
<td>1.5–1.9</td>
<td>5–10</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2.0–3.0</td>
<td>2.5–5</td>
<td>1.9–2.49</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>&gt;3.0</td>
<td>0</td>
<td></td>
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</tr>
</tbody>
</table>

References in parentheses.

Abbreviation: INR, international normalized ratio.
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remember which dosage they had taken the previous day. Dosages for odd and even days also become problematic at the end of a month for some months when an odd day may be followed by another odd day, the first of the month. Given the erratic response to vitamin K and the small therapeutic window, alternate dosing only serves to compound the difficulties in maintaining a smooth response.

Monitoring

Therapeutic range. Warfarin therapy is monitored through the use of the INR test, calculated from the PT measuring the intrinsic pathway factor activity. The therapeutic range of INR that is recommended for each indication for anticoagulation therapy is derived from studies of efficacy as well as safety with regard to its propensity to cause bleeding. For many indications for anticoagulation, efficacy is considerably reduced when the INR falls below 2, and the risk of bleeding begins to increase exponentially in patients in whom the INR is above 4 (74,75). Thus, the target INR of 2.5, with a range from 2 to 3, is the therapeutic range for many indications, as described above.

Frequency of monitoring. When anticoagulation is initiated, a baseline INR is usually obtained, and then daily monitoring is carried on until a therapeutic INR has been achieved. Monitoring is done every few days until the therapeutic INR appears sustained, which usually occurs within five to seven days. Then monitoring is usually done weekly, then biweekly, and finally every four weeks or less for patients who are relatively well controlled with regard to variability in INR results (76). In addition to the intensity of therapy, the stability of therapy is also important, as the time during which the INR fluctuates above the therapeutic range present periods of increased risk for hemorrhage.

Although there is some evidence to suggest that more frequent monitoring will be associated with greater efficacy and safety (77), the optimal frequency of INR testing to maintain patients within therapeutic range is not clear. In fact, it is thought by some that testing too frequently may lead to more variable control because of frequent dosage adjustment (66), without allowing for the three-day half-life of warfarin. Individual patients exhibit fluctuations of the INR with changes in diet, medications, clinical status, and medication adherence. Monitoring should be more frequent during these periods.

The time in therapeutic range (TTR) expresses the quality of anticoagulation management. This calculated value is not usually made available to patients or individual physicians, but can be monitored as a quality indicator for anticoagulation management. Older adults can be managed on anticoagulant therapy with the same TTR as other patients, despite the increased frequency of drug and disease interactions. Elderly patients managed on warfarin in an anticoagulation clinic had a similar TTR and rate of hemorrhage (78).

In all patients managed on anticoagulation, the TTR and stability of INR values have been found to improve after the three months of treatment (79). As a result, the rate of hemorrhage also declines after three months of therapy. Whether this is due to any physiologic change, or simply a survivor bias in which those individuals who are difficult to manage or who are likely to bleed do so early, is unclear. A meta-analysis of 33 trials and 4374 patient-years of anticoagulation therapy for venous thromboembolism found a 2.06% rate of bleeding, with fatal bleeding occurring in 0.37% (a case-fatality rate of 9.3%) in the first three months of therapy. After three months of therapy, the rate of major bleeding was 2.72% with a rate of fatal bleeding of 0.63% (case-fatality rate 9.1%). The rate of intracranial hemorrhage was 1.48 per 100 patient-years in the first three months, and 0.65 per 100 patient-years after three months of therapy (80).
Systems for monitoring. The interpretation and dosage adjustment based on monitoring of the INR can be accomplished manually or through the use of nomograms or computer programs and can be managed by primary care physicians, anticoagulation clinics or management services, or by patients themselves. The TTR across several studies of testing in physician’s offices ranges from 34% to 64% as compared with 61% to 92% for anticoagulation management services and 44% to 83% achieved in randomized controlled trials of warfarin (76,81). Although anticoagulation management systems appear to achieve a superior TTR, the frequency of testing was not comparable between studies, and often the patient samples studied were not randomized. However, a 60% reduction in both hemorrhagic and thromboembolic events has been observed across several studies of anticoagulation management systems (76). A recent study compared pharmacist-managed telephone versus in-office–based visits for anticoagulation management. All testing was done by venipuncture samples either at the clinic or at a local laboratory. The TTR, thromboembolic events, and frequency of emergency and hospital visits were similar for the two groups (82).

The INR can be determined through venipuncture samples in a laboratory or through use of point-of-care testing devices. Point-of-care PT/INR monitoring systems calculate a PT and the INR from measured thromboplastin clotting times on fingerstick samples. There are several devices available that can be used in offices, clinics, and by patients and visiting nurses. Point-of-care monitoring has been demonstrated to achieve a TTR of 56% to 93% (76). One study compared the cost of care for INR testing by home health nurses caring for 35 homebound elderly patients between obtaining the sample at the patients’ home and transporting them to a central laboratory, including materials, procedures, transportation, and labor, with a point-of-care PT monitoring system. The cost to obtain an INR test was $6.86 with the point-of-service model versus $17.30, with close agreement between the two values for those results falling below an INR of 3.5, but with greater disparity for higher values (83). Clearly patient selection for home monitoring and/or home adjustment of dosage using nomograms must be carefully considered.

Adverse Events

Bleeding. In clinical trials of anticoagulation for stroke prevention in patients with AF, the frequency of major bleeding events has been found to be 1.3% to 2.5% per year, with death due to bleeding in 0.4% annually, as compared with 1% per year for major bleeding events in the placebo and control groups (84–87). In these same clinical trials, intracranial hemorrhage (including both hemorrhagic strokes and subdural hematomas) occurred in 0.4% to 0.5% of patients, annually (84–87).

Warfarin skin necrosis. Although uncommon, warfarin skin necrosis is a serious adverse effect of warfarin, which is induced by a transient hypercoagulable state. It is often associated with the administration of large loading doses of warfarin and appears to affect individuals with congenital or acquired protein C or S deficiency (88,89). Affected individuals develop skin lesions within several days, which usually begin as an erythematous macule and progresses, if untreated, to an indurated lesion with purpuric regions, which ultimately becomes necrotic. Treatment with vitamin K (and withholding warfarin) appears to have an effect only when initiated early before irreversible skin changes occur (90).

Reversal

The ACCP (91) has developed guidelines for the management of over-anticoagulation of warfarin on the basis of the risk for bleeding at a given INR and the clinical setting. These
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Guidelines are based upon consensus and not clinical trials. Options for reversal in order of intensity include withholding warfarin therapy, administering vitamin K, administration of fresh frozen plasma to replenish clotting factors, and the administration of factor concentrates.

For patients in whom the INR is supratherapeutic but below 5 and there is no bleeding, the dose of warfarin may be reduced or withheld until the INR has fallen to within the therapeutic range. This may take three to five days (92). Warfarin should be withheld for all patients in whom the INR is greater than 6. In the elderly, as well as in those with a lower maintenance dose and with decompensated congestive heart failure or cancer, the fall in INR may occur more slowly than in other patients (93).

For patients without evidence of bleeding in whom the INR is 5 to less than 9, the ACCP (76) recommends omitting the next one to two doses, more frequent monitoring, and resumption of therapy at a lower dosage, or alternatively, omitting a dose and administering vitamin K at 1 to 2.5 mg orally. In the United States, oral vitamin K is usually available as 5 mg scored tablets, so that administration of a half tablet for an INR of 5 to 7 may be recommended, with the INR checked the next day, and the second half tablet taken if it has not fallen into the therapeutic range. For an INR above 7, a full 5 mg may be taken, and for an INR above 9, additional vitamin K is usually required, with the same regimen followed. There is no advantage in terms of timeliness of reversal to the use of SC vitamin K as opposed to oral. Vitamin K is fat soluble and readily absorbed. Oral vitamin K is preferred over SC or IV therapy as it was found to lower the INR more rapidly in asymptomatic patients who have INR values above the therapeutic range while receiving warfarin (94). Vitamin K administered by either method will begin to correct the INR within several hours but will not be completely effective until 24 hours. The ideal dosage is not clear, however, and the use of an excessive dosage will impair the ability to reinitiate anticoagulation with warfarin for several days.

The use of IV vitamin K has been associated with anaphylaxis. The risk is reduced by use of a slow infusion. For patients with serious bleeding and an elevated INR, the ACCP (91) recommends that warfarin be withheld, and 10 mg of vitamin K be given by slow IV infusion supplemented with fresh frozen plasma, prothrombin complex concentrate (which contains factors II, IX, and X, and low levels of factor VII) or recombinant factor VIIa, depending on the urgency of the situation. Patients with hemorrhages associated with anticoagulant therapy should otherwise be managed as a bleeding patient in whom anticoagulants are not a factor, including transfusion, supportive therapy, and invasive therapy.

DIRECT THROMBIN INHIBITORS AND NEW ANTICOAGULANT THERAPIES

The direct thrombin inhibitors interact directly with thrombin without the need of a cofactor such as antithrombin III or vitamin K, and inhibit both circulating and clot-bound thrombin. The first of this class of agents is hirudin. The direct thrombin inhibitors do not exhibit the nonspecific binding to plasma proteins seen with heparin and do not appear to be associated with immune thrombocytopenia. They are useful when anticoagulant therapy is indicated in a patient with HIT. Currently three direct thrombin inhibitors are approved for use in the United States—lepirudin, bivalirudin, and argatroban—all of which are parenterally administered. Several oral agents are in clinical development. Ximelagatran underwent significant development but was not released in the United States (87).
Hirudin and Lepirudin

Hirudin is a 65 amino acid polypeptide originally derived from the salivary glands of the medicinal leech. It forms a bivalent complex with thrombin, which is irreversible, and thus the anticoagulant effect cannot be reversed. Its half-life is 60 minutes after IV administration and 120 minutes after SC administration (48). It is renally excreted so it cannot be used in patients with renal insufficiency. The recombinant sulfated hirudin, lepirudin, is available for clinical use. It has a 10-minute half-life after IV infusion and is renally cleared, requiring dosage adjustment with renal insufficiency. Lepirudin is administered as an initial IV bolus of 0.4 mg/kg, up to a maximum of 110 kg, given over 15 to 20 seconds, then a continuous IV infusion of 0.15 mg/kg/hr. As with hirudin, monitoring with the aPTT is required for lepirudin with a desired therapeutic range of 1.5 to 2 times control values. An aPTT is obtained four hours after initiation of the infusion and dosages adjusted. If the aPTT is too high, the infusion is held for two hours and restarted at 50% of the prior dose. If the aPTT is too low, the dosage is increased in increments of 20% with retesting of the aPTT every four hours (95). When given along with warfarin, the aPTT should be at a target of 1.5 times the baseline value, and the infusion continued for four to five days to prevent a hypercoagulable state (48).

Bivalirudin

Bivalirudin is a synthetic 20 amino acid analog of hirudin. Bivalirudin also binds to thrombin but one bond is later cleaved, allowing some thrombin activity. This provides some reversibility and a superior safety profile as compared with hirudin, although it cannot be “reversed” with administration of another agent. Bivalirudin has a half-life of about 25 minutes, and is cleared by both the kidney and the liver, requiring some dosage adjustment with significant renal insufficiency. In a study (96,97) of its use in coronary angioplasty, hirudin was compared with heparin and was found to be superior (9.1% vs. 14.2%) with regard to the combined outcome of death, myocardial infarction, or revascularization at seven days. The rate of major bleeding was significantly less than that of heparin (3.9% vs. 9.8%; \( p < 0.001 \)). Bivalirudin was found to be comparable to heparin used in conjunction with a glycoprotein IIb/IIIa inhibitor for patients with acute coronary syndromes undergoing invasive treatment with regard to rates of ischemia and bleeding (23). Bivalirudin has become a popular anticoagulant in the cardiologists’ drug armamentarium.

Argatroban

Argatroban binds reversibly with thrombin and has a half-life of 45 minutes. It is a small compound that is metabolized in the liver, and cleared in less than an hour through biliary secretion. No dosage adjustment for renal function is required, but it must be used with caution in patients with hepatic disease. It is also administered as an infusion with aPTT monitoring for a therapeutic range of 1.5 to 3 (48). It is primarily used as an anticoagulant in patients with HIT or at risk of HIT who are undergoing percutaneous cardiac interventions.

HEMORRHAGIC RISK WITH ANTICOAGULANT THERAPY

Sites of Bleeding

Bleeding which occurs during the use of anticoagulant agents may be associated with a previously existing lesion, new pathology, or spontaneous hemorrhage. The morbidity and mortality associated with hemorrhage clearly relates to both the site of bleeding and the
Risk Factors for Bleeding

The most important factor with regard to the propensity to bleed from any site is the intensity of therapy (75, 91), with an INR greater than 4 markedly increasing risk, particularly for intracranial hemorrhage (75). Concurrent use of other medications which potentiate bleeding risk, particularly antiplatelet agents such as aspirin or clopidogrel, are commonly used in elderly patients with cardiovascular disease. Nonsteroidal anti-inflammatory agents commonly used for arthritis and pain in older adults also have antiplatelet activity and pose an increased risk for bleeding for this reason in addition to their association with peptic ulcer disease and gastritis.

Age appears to be an independent risk factor for major hemorrhage, although this remains controversial. Patients older than 75 years in the Stroke Prevention in Atrial Fibrillation trial who were treated with warfarin had a 4.2% rate of major bleeding per year as contrasted with the 1.7% for those under the age of 75 years (102). The rate of intracranial hemorrhage increases with advanced age, with a 40% increase per decade (99).

Several concurrent medical conditions also increase the risk for bleeding including patients with recent hemorrhage or a history of gastrointestinal hemorrhage, stroke, liver disease, and renal insufficiency (99, 103). Hypertension (103), stroke (75), and cancer (91) have also been associated with an increased risk of hemorrhage for patients treated with warfarin. A decision-analysis model used to define risk factors for gastrointestinal hemorrhage concluded that persons with spontaneous (not associated with nonsteroidal anti-inflammatory medications) upper gastrointestinal tract bleeding which has resolved, and who have been evaluated and treated for Helicobacter pylori, if appropriate, appear to have no increased risk of hemorrhage over people without a history of upper gastrointestinal hemorrhage (104).

Bleeding Risk Prediction Rules

Prediction rules can assist in assessing bleeding risk. The modified Outpatient Bleeding Risk Index (105) assigns one point each for: age 65 years and older; history of gastrointestinal bleeding; history of stroke; and one or more specific comorbid conditions (recent myocardial infarction, hematocrit of <30%, renal insufficiency with a creatinine of >1.5 mg/dL, or diabetes mellitus). A low risk for major bleeding (0 points) using this instrument confers a 2% risk within three months and 3% for 12 months; intermediate risk (1–2 points) confers a 5% three-month risk and a 12% 12-month risk; high risk (3–4 points) confers a 23% risk for major bleeding within three months and a 48% risk within 12 months. Using the Outpatient Bleeding Risk Index to stratify patients for risk, Beyth (106) undertook a randomized study of usual care versus a multicomponent intervention to prevent major bleeding complications in older patients receiving warfarin for treatment of a thromboembolic disease. The intervention consisted of patient education about warfarin, training to increase patient participation, self-monitoring of the prothrombin time, and nomogram-based management of warfarin dosing. At six months, the TTR for the intervention group was 56% versus 32% in controls, major bleeding was 5.6% versus 12% in controls, and death and thromboembolic complications were similar between the two groups.
A new bleeding risk model (107) for use in evaluating elderly AF patients for warfarin stroke prophylaxis was developed using data from 26,345 AF patients who were aged 65 years or more and had been discharged from the hospital following an episode of bleeding while receiving warfarin therapy. The model weighs the following variables in a formula to develop a risk score: older than 70 years, gender, remote bleeding, recent bleeding during the index hospitalization, alcohol or drug abuse, diabetes, anemia, and antiplatelet use. Bleeding rates were 0.9%, 2.0%, and 5.4%, respectively, for the groups with low, moderate, and high risk. This model can be individualized, but requires use of the formula that may be inconvenient in all clinical settings.

Quality of Life and Clinical Decision-Making

Warfarin continues to remain the mainstay of anticoagulant therapy for chronic use because it can be orally administered. Its efficacy in the prevention of thromboembolic disease has been demonstrated, and the risk associated with bleeding, quantified. Its use necessitates dietary oversight and restriction, frequent blood tests, physician communication, and vigilance regarding bleeding and trauma, all of which have an impact upon quality of life. A few studies have attempted to investigate these issues using various methodologies to quantify quality of life. One study used a Markov model decision analysis to determine whether anticoagulant therapy for prevention of stroke in patients with AF should be used in fallers. In an assessment that valued the impact of stroke higher than the impact from falls, patients with AF aged 65 years and older, of average stroke and falling risk, had an increase in their quality-adjusted life-years (QALY) with warfarin therapy (12.90 QALY per patient), as compared with aspirin therapy (11.17 QALY) or no therapy (10.15 QALY), as the stroke had a greater impact than falling (108).

Another study investigated patients’ quality of life estimates regarding three intensities of stroke and the use of various antithrombotic prophylactic treatments in elderly veterans with AF. This study demonstrated wide variability in patient attitudes and preferences regarding the tolerability of the disability associated with stroke (109). This variability in preference is similar to that identified in other studies of outcomes unrelated to the use of anticoagulants (110). Beyth reviews these studies and raises the issue of physician decision-making and their values, which weigh heavily in deciding to offer anticoagulation to a patient, in addition to the patient’s preferences in making these decisions (111). It is the responsibility of a physician to assess the individualized risks for thromboembolic events and hemorrhage in a given patient, and present these data to patients who can then express their preferences and values. Documentation of such discussions in which the risks and benefits are weighed is important. These decisions can be revisited as the risks and benefits change with the patient’s circumstances, particularly with advanced age.

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Anticoagulation in the Elderly


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Acute Pulmonary Embolism in the Elderly

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RATES OF DIAGNOSIS AND TRENDS IN THE DIAGNOSIS OF DEEP VENOUS THROMBOSIS AND PULMONARY EMBOLISM IN THE ELDERLY

Rates of diagnosis of deep venous thrombosis (DVT) in elderly patients (70 years or older) in the United States increased by 44% from 454 DVT/100,000 population in 1990 to 655 DVT/100,000 population in 1999 (1). DVT was diagnosed 4.7 times more frequently in elderly patients than in younger patients (20 to 69 years). Contrary to DVT, the rate of diagnosis of pulmonary embolism (PE) decreased from 370 PE/100,000 population in 1979 to 254 PE/100,000 population in 1990 and then remained constant from 1990 to 1999. The rates of diagnosis of DVT or PE in elderly men and women, and elderly blacks and whites were comparable (1). The diagnosis of PE in patients 70 years or older was 6.2 times the rate in younger patients.

DVT, based on hospital discharges, was diagnosed in 700 patients/100,000 population aged 70 to 89 years, 300/100,000 population aged 60 to 69 years, and in lower proportions among the population of younger people (1). Comparing the rate of DVT at each decade of age with the rate at age 20 to 29 years, the rate ratio increased exponentially up to age 89 years (Fig. 1) (1).

PE, based on hospital discharges, was diagnosed in 300 patients/100,000 population aged 70 to 89 years, 100/100,000 of the population aged 60 to 69 years, and in lower proportions among the population of younger people (1). Comparing the rate of PE at each decade of age with the rate at age 20 to 29 years, the rate ratio increased exponentially up to age 89 years (Fig. 2) (1). In patients aged 70 to 79 years, the rate of diagnosis of PE was 20.6 times the rate of diagnosis in patients aged 20 to 29 years. Many investigations indicate that the risk of venous thromboembolism increases with age (1–17).

Just as the risk of PE and DVT are age dependent, the estimated case fatality rate from PE is also strongly age dependent (18). The case fatality rate increased exponentially with age from 3.6% in patients aged 25 to 34 years to 17.4% in patients older than 85 years (18) (Fig. 3).
Figure 1  Rate ratios for the rate of diagnosis of DVT, comparing each decade of age with the rate at age 20 to 29 years. Rate ratios were averaged over 21 years. Between ages 20 to 29 and 80 to 89 years the rate ratios for the diagnosis of DVT increased exponentially. The 95% confidence intervals were too narrow to be displayed. *Abbreviation:* DVT, deep venous thrombosis. *Source:* From Ref. 1.

Figure 2  Rate ratios for the rate of diagnosis of PE, comparing each decade of age with the rate at age 20 to 29 years. Rate ratios were averaged over 21 years. Between ages 20 to 29 and 80 to 89 years the rate ratios for the diagnosis of PE increased exponentially. The 95% confidence intervals were too narrow to be displayed. *Abbreviation:* PE, pulmonary embolism. *Source:* From Ref. 1.
Acute Pulmonary Embolism in the Elderly

PREDISPOSING FACTORS IN ELDERLY PATIENTS

Age itself appears to be an important predisposing factor, although the illnesses associated with age, in fact, may be the true predisposing factors. Among patients aged 70 years and older, 67% were immobilized before the PE, and surgery preceded the PE in 44% (19). Malignancy was more frequent among patients aged 70 years and older than among younger patients, occurring in 26% (19).

SYNDROMES OF PE IN ELDERLY PATIENTS

The usual syndromes of PE are (1) pulmonary hemorrhage or infarction syndrome characterized by pleuritic pain or hemoptysis; (2) isolated dyspnea, unaccompanied by hemoptysis, pleuritic pain, or circulatory collapse; and (3) circulatory collapse. These syndromes were observed with comparable frequency among elderly patients and younger patients in the Prospective Investigation of Pulmonary Embolism Diagnosis (PIOPED) I (19), but among the elderly, the syndrome of isolated dyspnea was more frequent in PIOPED II (20). Among elderly patients, in contrast to younger patients, 11% did not show the usual syndromes (19). PE in these patients was suspected on the basis of unexpected radiographic abnormalities, which may have been accompanied by tachypnea or a history of thrombophlebitis. Unexplained radiographic abnormalities in elderly patients may be an important clue to the diagnosis of PE (19,21).

SYMPTOMS OF PE IN ELDERLY PATIENTS

In considering all elderly patients, including those who may have had prior cardiopulmonary disease, dyspnea and pleuritic pain were the most frequent symptoms (Table 1). Dyspnea occurred in 75% to 78% of elderly patients with PE, and pleuritic pain occurred in 33% to 51% (19,20). Hemoptysis occurred less frequently among patients aged 70 years and older than among younger patients in PIOPED I (19), but the rates of
hemothysis were similar in elderly and in younger patients in PIOPED II (20). Other symptoms occurred with comparable frequency among all age groups. Pleuritic pain was more frequent than hemothysis (19,20,22).

**SIGNS OF PE IN ELDERLY PATIENTS**

Among all patients aged 70 years and older, regardless of prior cardiopulmonary disease, tachypnea (respiratory rate ≥20/min) was the most frequent sign of PE. Tachypnea occurred in 74% in PIOPED I and 51% in PIOPED II (19,20) (Table 2). Tachycardia (heart rate >100/min) occurred in 29% and in 21% of elderly patients with PE in PIOPED I and PIOPED II. All signs occurred with a comparable frequency among all age groups.

**COMBINATIONS OF SYMPTOMS AND SIGNS IN ELDERLY PATIENTS**

Dyspnea or tachypnea occurred in 92% of all elderly patients in PIOPED I, including those with prior cardiopulmonary disease, but in only 77% in PIOPED II (19,20) (Table 3). Among patients with PE, therefore, some may not have even the most characteristic signs or symptoms, and this may reflect the severity of the PE. Among all patients with PE, dyspnea, tachypnea, or pleuritic pain occurred in 94% of patients older than 70 years in PIOPED I and in 87% in PIOPED II (19,20). If signs of DVT were added, 94% of patients older than 70 years in PIOPED I and 96% in PIOPED II had one or more of these findings. Combinations of signs and symptoms occurred with similar frequency in all age groups (19,20).
Table 2  Signs of Acute Pulmonary Embolism in the Elderly

<table>
<thead>
<tr>
<th>General</th>
<th>PIOPED I ≥70 yrs</th>
<th>PIOPED II ≥70 yrs</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>N = 72 %</td>
<td>N = 52–55 %</td>
</tr>
<tr>
<td>Tachypnea (≥20/min)</td>
<td>74</td>
<td>51</td>
</tr>
<tr>
<td>Tachycardia (&gt;100/min)</td>
<td>29</td>
<td>21</td>
</tr>
<tr>
<td>Diaphoresis</td>
<td>8</td>
<td>2</td>
</tr>
<tr>
<td>Cyanosis</td>
<td>3</td>
<td>0</td>
</tr>
<tr>
<td>Temperature &gt;38.5°C (&gt;101.3°F)</td>
<td>7</td>
<td>0</td>
</tr>
<tr>
<td>Cardiac examination (abnormal)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Increased P2&lt;sup&gt;a&lt;/sup&gt;</td>
<td>15</td>
<td>7</td>
</tr>
<tr>
<td>Right ventricular lift&lt;sup&gt;b&lt;/sup&gt;</td>
<td>—</td>
<td>4</td>
</tr>
<tr>
<td>Jugular venous distension</td>
<td>—</td>
<td>19</td>
</tr>
<tr>
<td>Third heart sound</td>
<td>7</td>
<td>—</td>
</tr>
<tr>
<td>Lung examination (abnormal)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Rales (crackles)</td>
<td>65</td>
<td>26</td>
</tr>
<tr>
<td>Wheezes</td>
<td>8</td>
<td>4</td>
</tr>
<tr>
<td>Rhonchi</td>
<td>—</td>
<td>6</td>
</tr>
<tr>
<td>Decreased breath sounds</td>
<td>—</td>
<td>29</td>
</tr>
<tr>
<td>Pleural friction rub</td>
<td>6</td>
<td>2</td>
</tr>
<tr>
<td>DVT signs&lt;sup&gt;c&lt;/sup&gt;</td>
<td>15</td>
<td>47</td>
</tr>
<tr>
<td>Homan’s Sign</td>
<td>4</td>
<td>—</td>
</tr>
</tbody>
</table>

<sup>a</sup>Data in 42 patients in PIOPED II.
<sup>b</sup>Data in 45 patients in PIOPED II.
<sup>c</sup>Edema, erythema, tenderness, or palpable cord.

Abbreviations: P2, pulmonary component of second sound; DVT, deep venous thrombosis.
Source: From Refs. 19,20.

Table 3  Combinations of Signs and Symptoms in All Elderly Patients with Acute Pulmonary Embolism

<table>
<thead>
<tr>
<th></th>
<th>PIOPED I N = 72 %</th>
<th>PIOPED II N = 52 %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dyspnea or tachypnea</td>
<td>92</td>
<td>77</td>
</tr>
<tr>
<td>Dyspnea or tachypnea or hemoptysis</td>
<td>92</td>
<td>—</td>
</tr>
<tr>
<td>Dyspnea or tachypnea or pleuritic pain&lt;sup&gt;a&lt;/sup&gt;</td>
<td>94</td>
<td>87</td>
</tr>
<tr>
<td>Dyspnea or tachypnea or signs of deep venous thrombosis</td>
<td>92</td>
<td>—</td>
</tr>
<tr>
<td>Dyspnea or tachypnea or pleuritic pain or signs of deep venous thrombosis&lt;sup&gt;a&lt;/sup&gt;</td>
<td>94</td>
<td>96</td>
</tr>
<tr>
<td>Dyspnea or tachypnea or radiographic atelectasis or parenchymal abnormality</td>
<td>100</td>
<td>—</td>
</tr>
<tr>
<td>Dyspnea or tachypnea or pleuritic pain or radiographic atelectasis or parenchymal abnormality&lt;sup&gt;a&lt;/sup&gt;</td>
<td>100</td>
<td>—</td>
</tr>
</tbody>
</table>

<sup>a</sup>The addition of hemoptysis did not improve the sensitivity of the combination for the detection of pulmonary embolism.

Tachypnea, respiratory rate ≥20/min.

Abbreviation: PIOPED, prospective investigation of pulmonary embolism diagnosis.
Source: From Refs. 19,20.
THE ELECTROCARDIOGRAM IN ELDERLY PATIENTS WITH PE

Among all elderly patients, some of whom had prior cardiopulmonary disease, nonspecific ST-segment or T-wave changes were the most frequent electrocardiographic abnormalities (19). Either or both occurred in 56% of patients aged 70 years and older (19) (Table 4). With the exception of left anterior hemiblock (left axis deviation) among patients aged 70 years and older, other electrocardiographic abnormalities occurred in 12% or fewer elderly patients. No difference in the frequency of any electrocardiographic abnormalities occurred among different age groups (19).

Among elderly patients with the pulmonary hemorrhage/infarction syndrome and no prior cardiopulmonary disease, the electrocardiogram was normal in 62% (22). If abnormal, the most frequent abnormalities were nonspecific ST-segment or T-wave changes (38%).

BLOOD GASES IN ELDERLY PATIENTS WITH PE

The partial pressure of oxygen in arterial blood (Pao2) was lower among elderly patients with PE than among younger patients (19). The Pao2 among elderly patients with PE, some of whom had prior cardiopulmonary disease, was 61 + 12 mmHg (mean ± standard deviation).

The alveolar–arterial oxygen difference (gradient) among elderly patients with PE was 47 + 14 mmHg, which was higher than among younger patients. The alveolar–arterial oxygen difference in normal adults increases with age (23–26).

Elderly patients with the pulmonary hemorrhage/infarction syndrome who had no prior cardiopulmonary disease had a higher pulmonary artery mean pressure (25 ± 9 mmHg) and lower Pao2 (64 + 10 mmHg) than patients younger than 40 years (22).

CHEST RADIOGRAPH AMONG ELDERLY PATIENTS WITH PE

The chest radiograph was normal in 4% of all elderly patients with PE, including those with prior cardiopulmonary disease (19). Atelectasis or pulmonary parenchymal abnormalities were the most frequent radiographic abnormalities (Table 5). All radiographic abnormalities occurred with a comparable frequency among all age groups.

Table 4  Electrocardiographic Findings in Elderly Patients with Acute Pulmonary Embolism (N = 57)

<table>
<thead>
<tr>
<th>Abnormality</th>
<th>≥70 yrs (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal</td>
<td>21</td>
</tr>
<tr>
<td>ST segment or T-wave changes</td>
<td>56</td>
</tr>
<tr>
<td>Left axis deviation</td>
<td>18</td>
</tr>
<tr>
<td>Left ventricular hypertrophy</td>
<td>12</td>
</tr>
<tr>
<td>Acute myocardial infarction pattern</td>
<td>12</td>
</tr>
<tr>
<td>Low-voltage QRS</td>
<td>9</td>
</tr>
<tr>
<td>Complete right bundle branch block</td>
<td>7</td>
</tr>
<tr>
<td>Right ventricular hypertrophy</td>
<td>4</td>
</tr>
<tr>
<td>Right axis deviation</td>
<td>2</td>
</tr>
<tr>
<td>Right atrial enlargement</td>
<td>2</td>
</tr>
<tr>
<td>Incomplete right bundle branch block</td>
<td>2</td>
</tr>
</tbody>
</table>
Among elderly patients with PE and no prior cardiopulmonary disease who had the pulmonary hemorrhage/infarction syndrome, the chest radiograph showed atelectasis or a pulmonary parenchymal abnormality in 82% (22). The central pulmonary artery appeared dilated in 29%. A normal chest radiograph was uncommon in elderly patients, with the pulmonary hemorrhage/infarction syndrome occurring in 6% (22).

**CLINICAL ASSESSMENT IN ELDERLY PATIENTS**

When physicians were 80–100% confident on the basis of clinical judgment and simple laboratory tests that PE was present in elderly patients, they were correct in 90% of the cases in a small sample of patients (9 of 10 patients) (19). When they believed that there was less than 20% likelihood of PE, they correctly excluded the diagnosis in 81% of patients. In most elderly patients, physicians were uncertain of the diagnosis, believing that there was a 20–79% chance of PE. The accuracy of clinical assessment was comparable among patients in all age groups (19).

**VENTILATION/PERFUSION LUNG SCANS IN ELDERLY PATIENTS**

The use of lung scans has decreased since mid 1980s (27). The utility of ventilation/perfusion lung scans among patients aged 70 years and older was comparable with that in younger patients (19). Among patients aged 70 years and older with ventilation/perfusion lung scans indicating a high probability of PE, 94% had PE (Table 6). The positive

<table>
<thead>
<tr>
<th>Table 6</th>
<th>Ventilation-Perfusion Scans in Elderly Patients with Acute Pulmonary Embolism</th>
</tr>
</thead>
<tbody>
<tr>
<td>&gt;70 yrs</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Number of patients</td>
</tr>
<tr>
<td>High</td>
<td>34/36</td>
</tr>
<tr>
<td>Intermediate</td>
<td>27/100</td>
</tr>
<tr>
<td>Low</td>
<td>10/71</td>
</tr>
<tr>
<td>Near normal/normal</td>
<td>1/8</td>
</tr>
</tbody>
</table>

*Westermark’s sign, prominent central pulmonary artery and decreased pulmonary vascularity.*
predictive value of all probabilities of ventilation/perfusion lung scans using original PIOPED criteria (28) was comparable in all age groups (19).

The sensitivity of ventilation/perfusion scans interpreted as a high probability of PE among patients aged 70 years and older was 47% (19). The specificity of ventilation/perfusion scans interpreted as a high probability of PE among patients aged 70 years and older was 99%.

Elderly patients with no prior cardiopulmonary disease who had the pulmonary hemorrhage/infarction syndrome tended to show more mismatched perfusion defects than patients younger than 40 years, regardless of whether the defects were large or moderate in size (22).

In patients with no prior cardiopulmonary disease, a high positive predictive value can be achieved with fewer mismatched perfusion defects than are required for a high-probability interpretation in patients with prior cardiopulmonary disease (29,30). Stratification according to the presence or absence of prior cardiopulmonary disease was particularly useful for the evaluation of ventilation-perfusion lung scans in patients aged 70 years and older, although only 23% of elderly patients had no prior cardiopulmonary disease. Among patients aged 70 years and older who had no prior cardiopulmonary disease, two or more mismatched large- or moderate-sized perfusion defects showed a sensitivity of 74%, a specificity of 100%, and a positive predictive value of 100% (31).

**COMPPLICATIONS OF PULMONARY ANGIOGRAPHY AMONG ELDERLY PATIENTS**

Major complications of pulmonary angiography occurred in 1% of 200 patients aged 70 years and older (19). Renal failure, either major or minor, was the most frequent complication of angiography among elderly patients. It occurred in 3% of patients aged 70 years and older (19). “Minor” complications of renal failure were important complications, although dialysis was not required. Patients with these complications showed either an elevation of the serum creatinine from previously normal levels to 2.1 mg/100 mL or more (range 2.1–3.5 mg/100 mL), or an increase in a previously abnormal serum creatinine level greater than 2 mg/100 mL.

Minor complications of prior angiography included urticaria, pulmonary edema requiring only diuretics, nausea and vomiting, arrhythmias that were not life threatening, hematomas, interstitial staining with contrast material, and narcotic overdose (19). Minor complications occurred in 7% of patients aged 70 years and older.

**CONTRAST-ENHANCED SPIRAL COMPUTED TOMOGRAPHY**

Contrast-enhanced spiral computed tomography (CT) can be particularly useful in elderly patients because it is noninvasive, although the risk of renal toxicity from contrast material remains (19). Both contrast enhanced multidetector CT pulmonary angiography and the combination of CT pulmonary angiography with CT venous phase imaging showed similar sensitivities and specificities among various age groups (32). Multidetector CT pulmonary angiography alone or in combination with CT venous phase, therefore, gives comparably valid results irrespective of age. Among 824 patients aged 18 years or older, multidetector CT angiography was inconclusive in 51 patients (6.2%) because of poor image quality (33). Excluding such inconclusive studies, sensitivity of CT angiography was 83% and specificity was 96%. Positive and negative predictive values were 96% with a concordantly high or low clinical assessment, 92% with an intermediate
clinical assessment, and nondiagnostic if clinical probability was discordant with the results of imaging (33). The combination of CT angiography with CT venous phase imaging of the veins of the pelvis and lower extremities was inconclusive in 87 patients (10.6%) because image quality of either the CT angiogram or CT venogram was poor. Sensitivity of the combination of CT angiography with CT venography for PE was 90% and specificity was 95%. The combination was also nondiagnostic if the clinical assessment was discordant with the results of imaging. The false negative rate of 17% for CT angiography alone indicates the need for additional information to exclude PE. The predictive value of either CT angiography or CT angiography in combination with CT venography was high with a concordant clinical assessment, but additional testing is necessary when clinical probability is inconsistent with the imaging results (33).

GADOLINIUM-ENHANCED MAGNETIC RESONANCE ANGIOGRAPHY

Magnetic resonance angiography (MRA) of the pulmonary vasculature has been hampered by a multitude of factors such as respiratory and cardiac motion artifacts, saturation problems, poor signal-to-noise ratio, long acquisition times, and limited spatial resolution (34). Intravenous gadolinium, a paramagnetic agent, gives additional enhancement of the blood signal.

The most appealing approach to the application of gadolinium-enhanced MRA is its potential use for showing intraluminal filling defects. The intraluminal filling defect is considered the characteristic that is diagnostic of PE (28,35). Data on the use of gadolinium-enhanced MRA for the diagnosis of acute PE are sparse. Gadolinium-enhanced MRA for the diagnosis of acute PE had a sensitivity that ranged from 77% to 100% and a specificity that ranged from 95% to 98% (36–39).

With the present state-of-the-art technology, it is likely that MRA would be most useful in patients with a strong suspicion of PE in whom results of less expensive tests are equivocal and radiographic contrast material or ionizing radiation are contraindicated.

Many elderly patients have a low glomerular filtration rate, and the U. S. Food and Drug Administration (FDA) has advised caution in the use of gadolinium containing contrast agents in such patients. In June 2006, the U.S. FDA issued an alert indicating that 25 cases of nephrogenic systemic fibrosis or nephrogenic fibrosing dermopathy (NSF/NFD) had been reported in patients with advanced renal failure (patients requiring dialysis or with a glomerular filtration rate <15 mL/min) and who received a gadolinium-containing contrast agent (40). In December 2006, the FDA further advised that some patients with only moderate renal disease (glomerular filtration rate <60 mL/min/m²) also developed NSF/NFD following exposure to gadolinium-containing contrast agents (41,42). Since 1997, when NSF/NFD was first reported, 215 cases have been identified worldwide among millions of patients who received gadolinium-containing contrast agents.

STRATEGIES OF DIAGNOSIS

The choice of diagnostic tests depends on the clinical probability of PE, condition of the patient, availability of diagnostic tests, risks of iodinated contrast material, radiation exposure, and cost (43). Recommendations were formulated on the basis of the results of PIOPED II (33) and other studies (44–46), albeit with continued reliance on the physician’s judgment. The PIOPED II investigators recommended stratification of all patients with suspected PE according to an objective probability assessment. A negative
dimerized plasmin fragment D (D-dimer) rapid enzyme-linked immunosorbent assay (ELISA) with a low or moderate probability clinical assessment can safely exclude PE. If PE is not excluded, most PIOPED II investigators recommended CT angiography in combination with CT venography, although CT angiography alone is an option. In patients with discordant findings on clinical assessment and CT imaging, further evaluation depends on clinical judgment. The following specific recommendations were made, and in general, are applicable to elderly patients (43).

RECOMMENDATIONS FOR CLINICAL ASSESSMENT

- Clinical assessment should be made by an objective method prior to imaging.

RECOMMENDATIONS FOR PATIENTS WITH LOW PROBABILITY CLINICAL ASSESSMENT

- Perform a D-dimer rapid ELISA.
- No further testing is required if D-dimer is normal.
- If D-dimer is positive, most PIOPED II investigators recommend CT angiography/CT venography.
- CT venography of only the femoral and popliteal veins is recommended to reduce radiation exposure.
- If CT angiography or CT angiography/CT venography is negative, treatment is unnecessary.
- With main or lobar pulmonary emboli on CT angiography, treatment is indicated.
- With segmental or subsegmental pulmonary emboli the certainty of the CT diagnosis should be reassessed.
- CT angiography or CT angiography/CT venography should be repeated, if image quality is poor.
- In patients with segmental or subsegmental pulmonary emboli, pulmonary scintigraphy, a single venous ultrasound in those evaluated by CT angiography only, serial venous ultrasound examinations (47,48) or pulmonary digital subtraction angiography are optional.

RECOMMENDATIONS FOR PATIENTS WITH A MODERATE PROBABILITY CLINICAL ASSESSMENT

- If D-dimer rapid ELISA is negative, no further testing is necessary, but a venous ultrasound or magnetic resonance venography is optional.
- If D-dimer is positive, most PIOPED II investigators recommend CT angiography/CT venography.
- Treatment with anticoagulants while awaiting the outcome of diagnostic tests may be appropriate, particularly if the tests cannot be obtained immediately (49).
- If either CT angiography or CT angiography/CT venography is negative, then no treatment is necessary, but a venous ultrasound is recommended for those with a negative CT angiogram alone.
- If either CT angiography or CT angiography/CT venography is positive, treatment is recommended.
Acute Pulmonary Embolism in the Elderly

• With segmental or subsegmental pulmonary emboli, the certainty of the CT diagnosis should be re-assessed and options followed according to recommendations for patients with a low probability clinical assessment.

RECOMMENDATIONS FOR PATIENTS WITH A HIGH PROBABILITY CLINICAL ASSESSMENT

• D-dimer testing need not be done because a negative D-dimer in a patient with a high probability clinical assessment may not exclude PE.
• Treat with anticoagulants while awaiting the outcome of diagnostic tests (49).
• Most PIOPED II investigators recommend CT angiography/CT venography.
• If CT angiography is negative and CT angiography/CT venography was not done or was technically inadequate, then a venous ultrasound or magnetic resonance venography is recommended.
• If either CT angiography or CT angiography/CT venography is negative, other options include serial venous ultrasound examinations, pulmonary digital subtraction angiography, and pulmonary scintigraphy.
• If either CT angiography or CT angiography/CT venography is positive, treatment is recommended.

RECOMMENDATIONS FOR OPTIONAL PATHWAYS

• A venous ultrasound prior to imaging with CT angiography or CT angiography/CT venography is optional and may guide treatment, if positive.

RECOMMENDATIONS FOR PATIENTS WITH ALLERGY TO IODINATED CONTRAST MATERIAL

• D-dimer with clinical assessment is recommended to exclude PE.
• Patients with mild iodine allergies may be treated with steroids prior to the CT imaging.
• Venous ultrasound and pulmonary scintigraphy are recommended as alternative diagnostic tests in patients with severe iodine allergy.
• Serial venous ultrasound and gadolinium-enhanced CT angiography are options.

RECOMMENDATIONS FOR PATIENTS WITH IMPAIRED RENAL FUNCTION

• D-dimer with clinical assessment is recommended to exclude PE.
• Venous ultrasound is recommended and, if positive, treatment is indicated.
• Pulmonary scintigraphy is recommended if venous ultrasound is negative.
• Serial venous ultrasound is an option.

ANTICOAGULANT THERAPY

Recommendations for prophylaxis and antithrombotic therapy for PE were made in the Sixth American College of Chest Physicians (ACCP) Consensus Conference on
Antithrombotic Therapy (49,50). Several studies found that the frequency of bleeding during warfarin therapy is higher in older patients, although this was not observed by some (51). In one study, the relative risk for major bleeding was 3.2 for patients aged 65 years or older (52). The risk of major hemorrhagic complications among patients of all ages with thromboembolic disease, treated with “less intense” warfarin, international normalized ratio (INR) is equal to 2 to 3, based on pooled data, was 1.7% (53).

Older patients also have a higher risk of bleeding from heparin than younger patients (54,55). The frequency of major hemorrhagic complications from heparin among patients of all ages treated for thromboembolic disease was 4.9%, based on pooled data (53). The frequency of major bleeding from heparin in high-risk patients (surgery within previous 14 days, history of peptic ulcer disease, gastrointestinal or genitourinary tract bleeding, or platelet count $< 150 \times 10^9/L$) was 10.8% (56). Among patients at low risk for bleeding, the frequency of major bleeding with heparin was 1.1% (56). Portions of the recommendations for treatment of DVT and PE are paraphrased from the Seventh ACCP Conference on Antithrombotic and Thrombolytic Therapy (49).

**TREATMENT OF DVT AND PE**

- For DVT and for PE low-molecular-weight heparin (LMWH) or IV unfractionated heparin are recommended for five days. In patients with DVT, subcutaneous unfractionated heparin may be used.
- Patients with a high clinical suspicion of DVT or PE should be treated with anticoagulants while awaiting the outcome of diagnostic tests.
- Vitamin K antagonists should be initiated together with LMWH or unfractionated heparin on the first treatment day and discontinuation of heparin when the INR is stable and greater than 2.
- If IV unfractionated heparin is chosen, it should be administered by continuous infusion with dose adjustment to achieve and maintain a partial thromboplastin time (aPTT) prolongation corresponding to plasma heparin levels from 0.3 to 0.7 IU/mL anti-Xa activity by the amidolytic assay. In patients requiring large daily doses of unfractionated heparin without achieving a therapeutic activated aPTT, the measurement of the anti-Xa level for dose guidance is recommended.
- In treatment with LMWH, routine monitoring of anti-factor Xa level is not necessary.
- In patients with acute DVT and in those with nonmassive acute PE, initial treatment with LMWH is preferred over unfractionated heparin.
- Patients with DVT may be treated as an outpatient if possible, and ambulated as tolerated.
- In patients with severe renal failure, the use of IV unfractionated heparin over LMWH is suggested.
- In patients with massive iliofemoral DVT at risk of limb gangrene due to venous occlusion, IV thrombolysis or venous thrombectomy is suggested.
- The placement of an inferior vena cava filter is suggested in patients with PE or DVT with a contraindication for, or a complication of, anticoagulant treatment as well as in those with recurrent thromboembolism despite adequate anticoagulation.
- For patients with a first episode of PE, proximal DVT, or calf vein DVT secondary to a transient (reversible) risk factor, long-term treatment with a vitamin K antagonist for three months over treatment for shorter periods is recommended.
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- For patients with a first episode of idiopathic DVT or PE, treatment with a vitamin K antagonist at least 6 to 12 months is recommended and considered for indefinite anticoagulant therapy.
- For patients with DVT or PE and cancer, LMWH for the first three to six months of long-term anticoagulant therapy is recommended. For these patients, anticoagulant therapy is recommended indefinitely or until the cancer is resolved.
- For patients with two or more episodes of objectively documented DVT, indefinite treatment is suggested.
- The dose of vitamin K antagonist should be adjusted to maintain a target INR of 2.5 (range, 2 to 3) for all treatment durations.
- Repeat testing with compression ultrasonography, for the presence or absence of residual thrombosis or measurement of plasma D-dimer, is suggested to assess the risk–benefit ratio of continuing such treatment.
- The use of an elastic compression stocking with a pressure of 30 to 40 mmHg at the ankle during two years after an episode of DVT is recommended.

THROMBOLYTIC THERAPY

Intracranial bleeding appears to be more common in elderly patients following thrombolytic therapy, based on experience following myocardial infarction (57). The average reported risk of major bleeding in patients of all ages who were administered tissue plasminogen activator (tPA) for acute PE was 14.7% (58). Among those pulmonary angiograms, major bleeding at the site of insertion of the catheter was 7% (58).

There has been considerable concern about whether thrombolytic agents are indicated in patients with right ventricular (RV) dysfunction from acute PE who are not in shock (59). Among stable patients with baseline RV hypokinesis, the mortality was 0% among 18 patients randomized to rtPA compared with 11% among 18 patients randomized to heparin (59). With these small numbers, there was no statistically significant difference in the death rate. However, the frequency of recurrent PE was greater in the group treated only with heparin. In a retrospective investigation of 64 patients with RV dysfunction who received thrombolytic therapy, compared with 64 who received heparin alone, the mortality was comparable in both groups and the rate of recurrent PE was the same in both groups (60).

Konstantinides and associates reported the clinical course of stable patients with submassive acute PE who were treated either with rtPA plus heparin or heparin alone (61). RV dysfunction was present in 31% of patients in both treatment arms. Mortality was comparable in both groups. “Rescue thrombolysis” was required in 23% of the patients in the heparin arm (61). The most appropriate indication for thrombolytic therapy in patients with PE is massive PE in patients who are hemodynamically unstable and have no contraindications to thrombolytic therapy (49).

The PIOPED II investigators found that in-hospital prognosis is good in patients with PE and RV enlargement providing they are not in shock, acutely ill, on ventilatory support, or had a recent myocardial infarction or life-threatening arrhythmia (62). Among 76 patients with RV enlargement who were treated with anticoagulants and/or inferior vena cava filters, in-hospital deaths from PE were 0 of 76 (0%) and all-cause mortality was 2 of 76 (2.6%). RV enlargement alone in patients with PE, therefore, does not appear to indicate a poor prognosis or be an indication for thrombolytic therapy in such stable patients.
CONCLUSION

In conclusion, the signs and symptoms known to occur among younger patients also occurred in elderly patients, although occasional exceptions were observed. Even among elderly patients, typical signs and symptoms occurred with sufficient frequency to suggest the possibility of PE in the differential diagnosis. In the absence of these signs and symptoms, unexplained radiographic abnormalities were important diagnostic clues. The recommended diagnostic approach is an objective clinical assessment followed by a rapid ELISA D-dimer. If these do not exclude PE, a CT pulmonary angiogram in combination with a CT venogram is the usual recommended approach, provided the patient has no contraindication to iodinated contrast material. Serial noninvasive leg tests in combination with ventilation/perfusion lung scans may eliminate the need for CT angiography in many elderly patients.

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Management of Peripheral Arterial Disease in the Elderly

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INTRODUCTION

Peripheral arterial disease (PAD) is chronic arterial occlusive disease of the lower extremities caused by atherosclerosis. PAD may cause intermittent claudication, which is pain or weakness with walking that is relieved with rest. The muscle pain or weakness after exercise occurs distal to the arterial obstruction. Since the superficial femoral and popliteal arteries are most commonly affected by atherosclerosis, the pain of intermittent claudication is most commonly localized to the calf. Atherosclerotic obstruction of the distal aorta and its bifurcation into the two iliac arteries may cause pain in the buttocks, hips, thighs, or the inferior back muscles as well as the calves.

The Rutherford classification of PAD includes seven stages (1). PAD is classified as stage 0 if the person is asymptomatic, stage 1 if the person has mild intermittent claudication, stage 2 if the person has moderate intermittent claudication, stage 3 if the person has severe intermittent claudication, stage 4 if the person has ischemic rest pain, stage 5 if the person has minor tissue loss, and stage 6 if the person has ulceration or gangrene (1).

Only one-half of elderly persons with documented PAD are symptomatic. Persons with PAD may not walk far or fast enough to induce muscle ischemic symptoms because of comorbidities such as pulmonary disease or arthritis, may have atypical symptoms unrecognized as intermittent claudication (2), may fail to mention their symptoms to their physician, or may have sufficient collateral arterial channels to tolerate their arterial obstruction. Women with PAD have a higher prevalence of leg pain on exertion and at rest, poorer functioning, and greater walking impairment from leg symptoms than men with PAD (3). Poorer leg strength in women contributes to poorer lower extremity functioning in women with PAD than in men with PAD (3). Upper extremity PAD will cause unequal blood pressure measurements in each arm. PAD patients also have a higher prevalence of cognitive impairment and erectile dysfunction.

If the arterial flow to the lower extremities cannot meet the needs of resting tissue metabolism, critical lower extremity ischemia occurs with pain at rest or tissue loss.
Critical ischemia causes rest pain in the toes or foot with progression to ulceration or gangrene. Chronic arterial insufficiency ulcers commonly develop at the ankle, heel, or leg. Mummified, dry, black toes or devitalized soft tissue covered by a crust is gangrene caused by ischemic infarction. Suppuration often develops with time, and dry gangrene changes to wet gangrene.

PHYSICAL EXAMINATION

The vascular physical examination includes (i) measurement of the blood pressure in both arms; (ii) palpation of the carotid pulses and listening for carotid bruits; (iii) auscultation of the abdomen and flank for bruits; (iv) palpation of the abdomen and notation of the presence of the aortic pulsation and its maximal diameter; (v) palpation of pulses at the brachial, radial, ulnar, femoral, popliteal, dorsalis pedis, and posterior tibial sites; and (vi) auscultation of both femoral arteries for femoral bruits (4).

The shoes and socks should be removed and the feet inspected. The color, temperature, and integrity of the skin should be evaluated and the presence of distal hair loss, trophic skin changes, hypertrophic nails, and ulcerations noted (4).

NONINVASIVE DIAGNOSIS

Persons with PAD of the lower extremities have reduced or absent arterial pulses. Noninvasive tests used to assess lower extremity arterial blood flow include measurement of ankle and brachial artery systolic blood pressures, characterization of velocity waveform, and duplex ultrasonography. Measurement of ankle and brachial artery systolic blood pressures using a Doppler stethoscope and blood pressure cuffs allows calculation of the ankle-brachial index (ABI), which is normally 0.9 to 1.2. An ABI of less than 0.9 is 95% sensitive and 99% specific for the diagnosis of PAD (5). The lower the ABI, the more severe the restriction of arterial blood flow, and the more serious the ischemia. ABIs of 0.6 to 0.9 usually correlate with mild-to-moderate intermittent claudication. ABIs of 0.4 to 0.6 usually correlate with severe intermittent claudication. With ABIs of 0.25 to 0.4, rest pain and tissue loss are often found. Patients with calcified arteries from diabetes mellitus or renal failure occasionally have relatively non-compressible arteries, leading to falsely elevated ABI values in the normal range.

In addition to measuring arterial pressure in nonpalpable arteries, Doppler ultrasound methods allow characterization of the flow versus time velocity waveform. Finding biphasic flow at the groin or monophasic flow more distally is evidence of arterial obstruction even when ABI measurements are falsely increased to normal levels because of calcification.

Duplex ultrasonography combines Doppler frequency measurements with two-dimensional images of blood vessels. The severity of flow restriction caused by an arterial stenosis can be accurately assessed by this most comprehensive noninvasive method (6).

Duplex ultrasonography, computed tomographic angiography, and magnetic resonance angiography are useful in assessing the anatomic location and severity of PAD and in selecting suitable candidates for endovascular or surgical revascularization (4).

Treadmill exercise testing with and without preexercise and postexercise ABIs helps differentiate claudication from pseudoclaudication in patients with exertional leg symptoms (4). Treadmill exercise testing may be useful to diagnose PAD with a normal
Management of Peripheral Arterial Disease in the Elderly

Table 1  Prevalence of Peripheral Arterial Disease

<table>
<thead>
<tr>
<th>Study (Ref.)</th>
<th>Prevalence</th>
</tr>
</thead>
<tbody>
<tr>
<td>360 men aged 60 yr (7)</td>
<td>16%</td>
</tr>
<tr>
<td>306 women aged 60 yr (7)</td>
<td>13%</td>
</tr>
<tr>
<td>158 persons aged 38–59 yr (8)</td>
<td>5.6%</td>
</tr>
<tr>
<td>161 persons aged 60–69 yr (8)</td>
<td>15.9%</td>
</tr>
<tr>
<td>294 persons aged 70–82 yr (8)</td>
<td>33.8%</td>
</tr>
<tr>
<td>2214 women aged ≥65 yr (9)</td>
<td>13.9%</td>
</tr>
<tr>
<td>2870 women aged ≥65 yr (9)</td>
<td>11.4%</td>
</tr>
<tr>
<td>467 men, mean age 80 yr (10)</td>
<td>20%&lt;sup&gt;a&lt;/sup&gt;</td>
</tr>
<tr>
<td>1444 women, mean age 81 yr (10)</td>
<td>13%&lt;sup&gt;a&lt;/sup&gt;</td>
</tr>
<tr>
<td>2589 men aged ≥55 yr (11)</td>
<td>16.9%</td>
</tr>
<tr>
<td>3861 women aged ≥55 yr (11)</td>
<td>20.5%</td>
</tr>
<tr>
<td>1160 men, mean age 80 yr (12)</td>
<td>32%&lt;sup&gt;a&lt;/sup&gt;</td>
</tr>
<tr>
<td>2464 women, mean age 81 yr (12)</td>
<td>26%&lt;sup&gt;a&lt;/sup&gt;</td>
</tr>
<tr>
<td>268 blacks, mean age 81 yr (13)</td>
<td>29%&lt;sup&gt;a&lt;/sup&gt;</td>
</tr>
<tr>
<td>71 Hispanics, mean age 81 yr (13)</td>
<td>24%&lt;sup&gt;a&lt;/sup&gt;</td>
</tr>
<tr>
<td>1310 whites, mean age 82 yr (13)</td>
<td>23%&lt;sup&gt;a&lt;/sup&gt;</td>
</tr>
<tr>
<td>386 men, mean age 72 yr (14)</td>
<td>26.7%&lt;sup&gt;a&lt;/sup&gt;</td>
</tr>
<tr>
<td>620 women, mean age 72 yr (14)</td>
<td>17.1%&lt;sup&gt;a&lt;/sup&gt;</td>
</tr>
<tr>
<td>6979 men and women, mean age 69 yr (15)</td>
<td>29%</td>
</tr>
</tbody>
</table>

<sup>a</sup>Symptomatic peripheral arterial disease.

resting ABI but a reduced postexercise ABI (4). Treadmill exercise testing may objectively document the magnitude of symptom limitation in patients with claudication (4).

**PREVALENCE**

The prevalence of PAD increases with age. Schroll and Munck reported that the prevalence of PAD was 16% in men and 13% in women aged 60 years (7) (Table 1). Criqui et al. showed that the prevalence of PAD was 5.6% in persons aged 38 to 59 years, 15.9% in persons aged 60 to 69 years, and 33.8% in persons aged 70 to 82 years (8) (Table 1). In the Cardiovascular Health Study, PAD was present in 13.9% of 2214 men aged 65 years and more and in 11.4% of 2870 women aged 65 years and more without cardiovascular disease (9) (Table 1). Symptomatic PAD was present in 20% of 467 men, mean age 80 years, and in 13% of 1444 women, mean age 81 years, living in the community and being seen in a geriatrics clinic (10) (Table 1). In the Rotterdam Study, PAD was present in 16.9% of 2589 men aged 55 years and more and in 20.5% of 3861 women aged 55 years and more (11) (Table 1). The prevalence of symptomatic PAD was 32% in 1160 men, mean age 80 years, and 26% in 2464 women, mean age 81 year, living in a nursing home (12) (Table 1). The prevalence of symptomatic PAD in persons living in a nursing home was also 29% in 268 blacks, mean age 81 years, 24% in 71 Hispanics, mean age 81 years, and 23% in 1310 whites, mean age 82 years (13) (Table 1). The prevalence of symptomatic PAD was 26.7% in 386 men, mean age 72 years, and 17.1% in 620 women, mean age 72 years, living in the community and being seen in a university general medicine clinic (14) (Table 1). The prevalence of PAD in 6979 men and women, mean age 69 years, screened for PAD by an ABI because they were aged 70 years or older or because they were aged 50 to 69 years with a history of cigarette smoking or
diabetes mellitus was 29% (15) (Table 1). Among these patients with PAD, classic claudication was present in only 11% (15).

**RISK FACTORS**

Modifiable risk factors that predispose to PAD include cigarette smoking (7,10,14,16–23), diabetes mellitus (7,10,14,16–24), hypertension (7,10,14,16,20–23,25,26), dyslipidemia (7,10,14,16,18–24,27–29), increased plasma homocysteine levels (30–33), and hypothyroidism (34). Table 2 indicates that significant independent risk factors for PAD in 467 men, mean age 80 years, and in 1444 women, mean age 81 years, living in the community and seen in an academic geriatrics practice were age (odds ratio = 1.05 for each one-year increase in age in men and 1.03 for each one-year increase in age in women), current cigarette smoking (odds ratio = 2.6 for men and 4.6 for women), systolic or diastolic hypertension (odds ratio = 2.2 for men and 2.8 for women), diabetes mellitus (odds ratio = 6.1 for men and 3.6 for women), serum high-density lipoprotein (HDL) cholesterol (odds ratio = 0.95 for each 1 mg/dL increase in men and 0.97 for each 1 mg/dL increase in women), and serum low-density lipoprotein (LDL) cholesterol (odds ratio = 1.02 for each 1 mg/dL increase in men and in women) (10).

In 147 men and women with PAD and 373 men and women without PAD, mean age 81 years, plasma homocysteine was a significant independent risk factor for PAD with an odds ratio of 1.13 for each 1 μmol/L increase (33). In 249 men and women, mean age 79 years, the prevalence of PAD was significantly higher in persons with subclinical hypothyroidism (14 of 18 persons or 78%) than in persons with euthyroidism (40 of 231 persons or 17%) (34).

**COEXISTENCE OF OTHER ATHEROSCLEROTIC DISORDERS**

PAD coexists with other atherosclerotic disorders (Table 3) (14,23,35–40). In a study of 1886 men and women, mean age 81 years, 270 of 468 persons (58%) with PAD had coexistent coronary artery disease (CAD) and 159 of 468 persons (34%) with PAD had prior ischemic stroke (35) (Table 3). In a study of 1802 men and women, mean age 80 years, living in the community and seen in an academic geriatrics practice, 161 of 236 persons...
(68%) with PAD had coexistent CAD and 100 of 236 persons (42%) with PAD had coexistent prior ischemic stroke (36) (Table 3).

In 924 men, mean age 80 years, the prevalence of PAD was 1.5 times significantly higher in 336 men with mitral annular calcium than in 588 men without mitral annular calcium (43% vs. 28%) (37) (Table 3). In 1881 women, mean age 81 years, the prevalence of PAD was 1.6 times significantly higher in 985 women with mitral annular calcium than in 896 women without mitral annular calcium (31% vs. 19%) (37) (Table 3).

In 989 men, mean age 80 years, the prevalence of PAD was 1.6 times significantly higher in 141 men with aortic stenosis than in 848 men without aortic stenosis (48% vs. 30%) (38) (Table 3). In 1998 women, mean age 81 years, the prevalence of PAD was 1.7 times significantly higher in 321 women with aortic stenosis than in women without aortic stenosis (39% vs. 23%) (38) (Table 3).

In 279 men and women, mean age 71 years, with documented PAD and in 218 men and women, mean age 70 years, without PAD with normal ABIs undergoing coronary angiography for suspected CAD, the prevalence of obstructive CAD was significantly higher in persons with PAD (98%) than in persons without PAD (81%) (23) (Table 3). The prevalence of left main CAD was significantly higher in persons with CAD (18%)

### Table 3  Coexistence of Peripheral Arterial Disease With Other Atherosclerotic Disorders in Older Persons

<table>
<thead>
<tr>
<th>Study (Ref.)</th>
<th>Result</th>
</tr>
</thead>
<tbody>
<tr>
<td>1886 persons, mean age 81 yr (35)</td>
<td>If PAD was present, 58% had coexistent CAD and 34% had prior ischemic stroke</td>
</tr>
<tr>
<td>1802 persons, mean 80 yr (36)</td>
<td>If PAD was present, 68% had coexistent CAD and 42% had prior ischemic stroke</td>
</tr>
<tr>
<td>924 men, mean age 80 yr (37)</td>
<td>PAD was 1.5 times higher in men with mitral annular calcium than in men without mitral annular calcium</td>
</tr>
<tr>
<td>1881 women, mean age 81 yr (37)</td>
<td>PAD was 1.6 times higher in women with mitral annular calcium than in women without mitral annular calcium</td>
</tr>
<tr>
<td>989 men, mean age 80 yr (38)</td>
<td>PAD was 1.6 times higher in men with aortic stenosis than in men without aortic stenosis</td>
</tr>
<tr>
<td>1998 women, mean age 81 yr (38)</td>
<td>PAD was 1.7 times higher in women with aortic stenosis than in women without aortic stenosis</td>
</tr>
<tr>
<td>279 persons with PAD, mean age 71 yr, undergoing coronary angiography for suspected CAD (23)</td>
<td>Obstructive CAD was present in 98% of persons, left main CAD in 18% of persons, and 3- or 4-vessel CAD in 63% of persons</td>
</tr>
<tr>
<td>218 persons without PAD, mean age 70 yr, undergoing coronary angiography for suspected CAD (23)</td>
<td>Obstructive CAD was present in 82% of persons, left main CAD in &lt;1% of persons, and 3- or 4-vessel CAD in 11% of persons</td>
</tr>
<tr>
<td>1006 persons, mean age 72 yr (14)</td>
<td>If PAD was present, 63% had coexistent CAD, and 43% had prior ischemic stroke</td>
</tr>
<tr>
<td>336 patients, mean age 73 yr (39)</td>
<td>CAD was present in 75% of patients with a decreased ABI and in 29% of age- and gender-matched patients with a normal ABI</td>
</tr>
<tr>
<td>273 patients, mean age 71 yr, with CAD (40)</td>
<td>The lower the ABI, the higher the prevalence of 3- or 4-vessel CAD</td>
</tr>
</tbody>
</table>

**Abbreviations**: PAD, peripheral arterial disease; CAD, coronary artery disease.
than in persons without CAD (<1%) (23) (Table 3). The incidence of three-vessel or four-vessel CAD was significantly higher in persons with PAD (63%) than in persons without PAD (11%) (23) (Table 3).

In 1006 men and women, mean age 72 years, if PAD was present, 63% had coexistent CAD, and 43% had prior ischemic stroke (14) (Table 3). In 118 patients, mean age 73 years, with a decreased ABI, the prevalence of CAD was 75%, whereas in 118 age-matched and gender-matched patients with a normal ABI, the prevalence of CAD was 29% (39) (Table 3). The prevalence of aortic valve calcium or mitral annular calcium was also higher in the patients with a decreased ABI (69%) than in the patients with a normal ABI (36%) (39) (Table 3).

In 273 patients, mean age 71 years, with CAD, the lower the ABI, the higher the prevalence of three-vessel or four-vessel CAD (40) (Table 3). Patients with PAD also have a higher prevalence of left ventricular systolic dysfunction than patients without PAD (41).

CARDIOVASCULAR MORTALITY AND MORBIDITY

Persons with PAD are at increased risk for all-cause mortality, cardiovascular mortality, and cardiovascular events (18, 42–50). At 10-year follow-up of 565 men and women, mean age 66 years, PAD significantly increased the risk of all-cause mortality (relative risk = 3.1), mortality from cardiovascular disease (relative risk = 5.9), and mortality from CAD (relative risk = 6.6) (42). At four-year follow-up of 1492 women, mean age 71 years, an ABI of 0.9 or less was associated with a relative risk of 3.1 for all-cause mortality after adjustment for age, smoking, and other risk factors (45).

In a prospective study of 291 men and women, mean age 82 years, with PAD, CAD was present in 160 persons (55%) (44). Silent myocardial ischemia detected by 24-hour ambulatory electrocardiography was present in 60 of 160 persons (38%) with PAD and CAD and in 26 of 131 persons (20%) with PAD and no clinically evident CAD (44). At 43-month follow-up, new coronary events developed in 54 of 60 persons (90%) with PAD, CAD, and silent myocardial ischemia and in 59 of 100 persons (59%) with PAD, CAD, and no silent myocardial ischemia (44). New coronary events also developed in 18 of 26 persons (69%) with PAD, no CAD, and silent myocardial ischemia and in 34 of 105 persons (32%) with PAD, no CAD, and no silent myocardial ischemia (44).

A pooled analysis of mortality in eight, large, randomized percutaneous coronary intervention (PCI) trials of 19,867 patients showed that the presence of PAD was associated with higher rates of post-PCI death and myocardial infarction (50). PAD was an independent predictor of short-term and of long-term mortality (50). Dipyridamole thallium scintigraphy also has prognostic value in the preoperative assessment of patients with PAD undergoing vascular surgery (51).

RISK FACTOR MODIFICATION

Continuing smoking increases the risk of amputation in patients with intermittent claudication (52). Patency in lower extremity bypass grafts is also worse in smokers than in nonsmokers (53). Smoking cessation reduces the progression of PAD to critical leg ischemia and reduces the risk of myocardial infarction and death from vascular causes (54). Smoking cessation programs should be strongly encouraged in persons with PAD (Table 4).

Approaches to smoking cessation include use of nicotine patches or nicotine polacrilex gum, which are available over the counter (55). If this therapy is unsuccessful,
nicotine nasal spray or treatment with the antidepressant buproprion should be considered (55,56). A nicotine inhaler may also be used (57). The dosage and duration of treatment of each of these pharmacotherapies are discussed in detail elsewhere (57). Concomitant behavioral therapy may also be needed (58). Repeated physician advice is very important in the treatment of smoking addiction.

Hypertension should be adequately controlled to decrease cardiovascular mortality and morbidity in persons with PAD (25,26,59–61) (Table 4). The blood pressure should be reduced to less than 140/90 mmHg and to less than 130/80 mmHg in patients with diabetes mellitus or chronic renal insufficiency. In the Heart Outcomes Prevention Evaluation (HOPE) Study, 1715 persons had symptomatic PAD, and 2118 persons had asymptomatic PAD with an ABI less than 0.9 (60). In the HOPE Study, compared with placebo, ramipril 10 mg daily significantly reduced cardiovascular events by 25% in persons with symptomatic PAD (60). In this study, ramipril reduced the absolute incidence of cardiovascular events by 5.9% in persons with asymptomatic PAD and by 2.3% in persons with a normal ABI (62). In the HOPE Study, the antihypertensive properties of ramipril did not completely account for the observed risk reduction (60).

Among persons with PAD in the Appropriate Blood Pressure Control in Diabetes trial, the incidence of cardiovascular events in persons treated with antihypertensive drug therapy with enalapril or nisoldipine was 13.6% if the mean blood pressure was reduced to 128/75 mmHg versus 38.7% if the mean blood pressure was reduced to 137/81 mmHg (61).

Elderly persons with diabetes mellitus and PAD and no CAD have a 1.5 times higher incidence of new coronary events than elderly nondiabetics with PAD and prior myocardial infarction (62). The higher the hemoglobin A1c levels in patients with diabetes mellitus and PAD, the higher the prevalence of severe PAD (63). Diabetes mellitus should be treated with the hemoglobin A1c level decreased to less than 7% to decrease the incidence of myocardial infarction (64). The blood pressure should be reduced to less than 130/80 mmHg in elderly persons with PAD and diabetes mellitus (59,61,65). Elderly diabetics with PAD should also be treated with statins (66) and the serum LDL cholesterol reduced to less than 70 mg/dL (67).

Treatment of dyslipidemia with statins has been documented to reduce the incidence of mortality, cardiovascular events, and stroke in persons with PAD with and without CAD (28,29,66–73). At five-year follow-up of 4444 men and women with CAD and hypercholesterolemia in the Scandinavian Simvastatin Survival Study, compared with
placebo, simvastatin significantly decreased the incidence of intermittent claudication by 38% (68).

In a study of 264 men and 396 women, mean age 80 years, with symptomatic PAD and a serum LDL cholesterol of 125 mg/dL or higher, 318 of 660 persons (48%) were treated with a statin and 342 of 660 persons (52%) with no lipid-lowering drug (73). At 39-month follow-up, treatment with statins caused a significant independent reduction in the incidence of new coronary events of 58%, of 52% in persons with prior myocardial infarction, and of 59% in persons with no prior myocardial infarction (73).

In the Heart Protection Study, 6748 of the 20,536 persons (33%) had PAD (69). At five-year follow-up, treatment with simvastatin 40 mg daily caused a significant 19% relative reduction and a 6.3% absolute reduction in major cardiovascular events independent of age, gender, or serum lipids levels (69). These data favor administration of statins to elderly persons with PAD regardless of serum lipids levels.

On the basis of the available data, elderly persons with PAD and hypercholesterolemia should be treated with statins to reduce cardiovascular mortality and morbidity and progression of PAD (28,29,66–73) and to improve exercise time until intermittent claudication (74–76) (Table 4). Since lipid-lowering therapy is underutilized in persons with PAD (77,78), intensive educational programs are needed to educate physicians to use lipid-lowering therapy in elderly persons with cardiovascular disease and dyslipidemia (78–80). On the basis of data from the Heart Protection Study, persons with PAD should be treated with statins regardless of age, gender, or initial serum lipids levels (69).

Increased plasma homocysteine level is a risk factor for PAD (30–33). Reduction of increased plasma homocysteine levels can be achieved by administering a combination of folic acid, vitamin B6, and vitamin B12. However, we do not have double-blind, randomized, placebo-controlled data showing that reduction of increased plasma homocysteine levels will reduce coronary events and slow progression of PAD in elderly persons with PAD.

Hypothyroidism is a risk factor for PAD (34). Elderly persons with clinical or subclinical hypothyroidism should be treated with l-thyroxine to decrease the development of CAD (81) and possibly of PAD (34). There is no evidence showing that treatment with l-thyroxine will reduce the development of PAD or improve symptoms.

**ANTIPLATELET DRUGS**

Antiplatelet drugs that have been shown to decrease the incidence of vascular death, nonfatal myocardial infarction, and nonfatal stroke in persons with PAD are aspirin, ticlodipine, and clopidogrel (82). Aspirin and dipyridamole have not been shown to be more efficacious than aspirin alone in the treatment of persons with PAD (82). Oral platelet glycoprotein IIb/IIIa inhibitors have been shown to increase mortality in the treatment of persons with CAD and have not been investigated in the treatment of persons with PAD (83). Adverse hematologic effects associated with ticlodipine limit the use of this drug in the treatment of elderly persons with PAD (84).

Thromboxane A2 induces platelet aggregation and vasoconstriction. Aspirin decreases the aggregation of platelets exposed to thrombogenic stimuli by inhibiting the cyclooxygenase enzyme reaction within the platelet and thereby blocking the conversion of arachidonic acid to thromboxane A2 (85). Clopidogrel is a thienopyridine derivative that inhibits platelet aggregation by inhibiting the binding of adenosine 5'-diphosphate to its platelet receptor (86).
The Antithrombotic Trialists’ Collaboration Group (ATCG) reported a meta-analysis of 26 randomized studies of 6263 persons with intermittent claudication due to PAD (82). At follow-up, the incidence of vascular death, nonfatal myocardial infarction, and nonfatal stroke was 6.4% in patients randomized to antiplatelet drugs versus 7.9% in the control group, a significant reduction of 23% caused by antiplatelet therapy. The reductions are significant for all subgroups.

The ATCG reported a meta-analysis of 12 randomized studies of 2497 persons with PAD undergoing peripheral arterial grafting (82). At follow-up, the incidence of vascular death, nonfatal myocardial infarction, and nonfatal stroke was 5.4% in persons randomized to antiplatelet drugs versus 6.5% in the control group, a significant reduction of 22% caused by antiplatelet therapy.

The ATCG also reported a meta-analysis of four randomized studies of 946 persons with PAD undergoing peripheral angioplasty (82). At follow-up, the incidence of vascular death, nonfatal myocardial infarction, and nonfatal stroke was 2.5% in patients randomized to antiplatelet drugs versus 3.6% in the control group, a significant reduction of 29% caused by antiplatelet therapy.

If one combines the 42 randomized studies of 9706 patients with intermittent claudication, peripheral arterial grafting, or peripheral angioplasty, the incidence of vascular death, nonfatal myocardial infarction, and nonfatal stroke at follow-up was significantly decreased by 23% by antiplatelet drugs, with similar benefits among patients with intermittent claudication, those having peripheral arterial grafting, and those having peripheral angioplasty (82). These data favor the use of aspirin in men and women with PAD (82) (Table 4).

### Aspirin

Table 5 shows the efficacy of different doses of aspirin in reducing the incidence of vascular death, nonfatal MI, and nonfatal stroke in high-risk persons (82). Since aspirin doses greater than 150 mg daily do not reduce vascular death, nonfatal myocardial infarction, and nonfatal stroke more than does a dose of 75 to 150 mg daily and cause more gastrointestinal bleeding than the lower doses, this author prefers an aspirin dose of 81 mg daily in treating elderly persons with atherosclerotic vascular disease.

### Clopidogrel

In the Clopidogrel versus Aspirin in Patients at Risk for Ischaemic Events (CAPRIE) trial, 5795 persons with PAD were randomized to clopidogrel 75 mg daily and 5797 persons with PAD were randomized to aspirin 325 mg daily (87). At 1.9-year follow-up, the

<table>
<thead>
<tr>
<th>Table 5</th>
<th>Efficacy of Aspirin Doses in Decreasing Vascular Death, Nonfatal Myocardial Infarction, and Nonfatal Stroke in High-Risk Patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aspirin dose</td>
<td>Decrease in vascular death, myocardial infarction, or stroke</td>
</tr>
<tr>
<td>500–1500 mg (34 trials)</td>
<td>19%</td>
</tr>
<tr>
<td>160–325 mg (19 trials)</td>
<td>26%</td>
</tr>
<tr>
<td>75–150 mg (12 trials)</td>
<td>32%</td>
</tr>
<tr>
<td>&lt;75 mg (3 trials)</td>
<td>13%</td>
</tr>
</tbody>
</table>

**Source:** From Ref. 82.
annual incidence of vascular death, nonfatal myocardial infarction, and nonfatal stroke was 3.7% in persons randomized to clopidogrel versus 4.9% in persons randomized to aspirin, a 24% significant decrease with the use of clopidogrel (87).

On the basis of these data, it is reasonable to conclude that clopidogrel is superior to aspirin in the management of patients with PAD. On the basis of these data, the author also recommends the use of clopidogrel 75 mg daily in the treatment of patients with PAD (Table 4). However, clopidogrel is much more expensive than aspirin. In a vascular surgery clinic, 501 of 506 persons (83%) with PAD were treated with aspirin or clopidogrel (88).

ORAL ANTICOAGULANTS

In the Dutch Bypass Oral Anticoagulants or Aspirin Study, 2690 persons were randomized after infrainguinal bypass surgery to aspirin 80 mg daily or to oral anticoagulation with phenprocoumon or acenocoumarol to maintain an international normalized ratio of 3.0 to 4.5 (89). At 21-month follow-up, there was no significant difference between the two treatments in the primary outcome of infrainguinal graft occlusion (89). There was no significant difference between the two treatments in the secondary outcomes of myocardial infarction, stroke, amputation, or vascular death (89). However, persons treated with oral anticoagulant therapy had 1.96 times more major bleeding episodes than persons treated with oral aspirin (89). The American College of Cardiology/American Heart Association (ACC/AHA) guidelines state that oral anticoagulant therapy with warfarin should not be given to reduce the risk of adverse cardiovascular ischemic events in persons with atherosclerotic lower extremity PAD (4).

ANGIOTENSIN-CONVERTING ENZYME INHIBITORS

Data from the HOPE Study showed that ramipril 10 mg daily significantly decreased cardiovascular events in persons with symptomatic PAD and in persons with asymptomatic PAD (60). Angiotensin-converting enzyme inhibitors as well as statins also have many pleotropic effects to account for their vascular protective properties beyond their primary mode of action including inhibition of cellular proliferation, restoration of endothelial activity, inhibition of platelet reactivity, and an antioxidant potential (90). The ACC/AHA guidelines recommend treating persons with PAD with angiotensin-converting enzyme inhibitors unless there are contraindications to the use of these drugs to reduce cardiovascular mortality and morbidity (91) (Table 4).

β BLOCKERS

Persons with PAD are at increased risk for developing new coronary events (18,42–50). Many physicians have been reluctant to use β blockers in persons with PAD because of concerns that β blockers will aggravate intermittent claudication. However, a meta-analysis of 11 randomized controlled studies found that β blockers do not adversely affect walking capacity or the symptoms of intermittent claudication in persons with mild-to-moderate PAD (92).

An observational study was performed in 575 men and women, mean age 80 years, with symptomatic PAD and prior myocardial infarction (93). Of the 575 persons, 85 persons (15%) had contraindications to the use of β blockers. Of the 490 persons without contraindications to the use of β blockers, 257 persons (52%) were treated with β blockers. Adverse effects causing cessation of β blockers occurred in 31 of the 257 persons (12%).

At 32-month follow-up, use of β blockers caused a 53% significant independent decrease in the incidence of new coronary events in elderly persons with PAD and prior myocardial infarction (93). In a vascular surgery clinic, 301 of 364 persons (83%) with PAD and CAD were treated with β blockers (88). β Blockers should be used to treat CAD in patients with PAD in the absence of contraindications to these drugs (Table 4).

STATINS

On the basis of data from the Heart Protection Study, persons with PAD should be treated with statins regardless of age, gender, or initial serum lipids levels (69) (Table 4). Three double-blind, randomized, placebo-controlled studies have also demonstrated that statins improve walking performance in persons with PAD (Table 6) (74–76).

In a study of 69 persons, mean age 75 years, with intermittent claudication, a mean ABI of 0.63, and a serum LDL cholesterol of 125 mg/dL or higher, 3 of 34 persons (9%) treated with simvastatin and six of 35 persons (17%) treated with placebo died before the one-year study was completed (74). Compared with placebo, simvastatin significantly increased the treadmill exercise time until the onset of intermittent claudication by 24% at six months and by 42% at one year after therapy (Table 6) (74).

In a study of 354 persons, mean age 68 years, with intermittent claudication and hypercholesterolemia, at one-year follow-up, compared with placebo, atorvastatin 80 mg daily significantly improved pain-free treadmill walking distance by 40% and significantly improved community-based physical activity (Table 6) (75). In a study of 86 persons, mean age 67 years, with intermittent claudication and hypercholesterolemia, at six-month follow-up, compared with placebo, simvastatin 40 mg daily significantly improved pain-free walking distance and total walking distance on a treadmill, significantly improved the mean ABI at rest and after exercise, and significantly improved symptoms of claudication (Table 6) (76).

Statin use is also associated with superior leg functioning independent of cholesterol levels and other potential confounders (94). The data suggest that non-cholesterol-lowering properties of statins may favorably influence functioning in persons with and without PAD (94).

Table 6  Effects of Statins on Walking Performance in Patients With Intermittent Claudication

<table>
<thead>
<tr>
<th>Study (Ref.)</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>69 persons, mean age 75 yr, with intermittent claudication and hypercholesterolemia (74)</td>
<td>Compared with placebo, simvastatin 40 mg daily significantly increased treadmill exercise time until the onset of intermittent claudication by 24% at 6 mos and by 42% at 1 yr.</td>
</tr>
<tr>
<td>354 persons, mean age 68 yr, with intermittent claudication and hypercholesterolemia (75)</td>
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</tr>
<tr>
<td>86 persons, mean age 67 yr, with intermittent claudication and hypercholesterolemia (76)</td>
<td>At 6-mo follow-up, compared with placebo, simvastatin 40 mg daily significantly increased pain-free walking distance and total walking distance on a treadmill, the mean ankle-brachial index at rest and after exercise, and symptoms of claudication.</td>
</tr>
</tbody>
</table>
DRUGS TO INCREASE WALKING DISTANCE

Chelation therapy has been demonstrated to be ineffective in the therapy of PAD (95). Numerous drugs have been shown to be ineffective in improving walking distance in persons with intermittent claudication (96,97). Beraprost sodium, an orally active prostaglandin I2 analogue, was demonstrated to be no more effective than placebo in persons with intermittent claudication (98). Naftidrofuryl (99) and propionyl levocarnitine (100) have been reported to improve exercise-walking distance in persons with intermittent claudication but have not been approved for use in the United States (96).

Two drugs, pentoxifylline and cilostazol, have been approved by the United States Food and Drug Administration for symptomatic treatment of intermittent claudication. However, many studies have found no consistent improvement with pentoxifylline in patients with intermittent claudication in comparison with placebo (101–103). In a vascular surgery clinic, 301 of 301 persons (100%) with intermittent claudication were treated with cilostazol or pentoxifylline (88).

Cilostazol inhibits phosphodiesterase type 3, increasing intracellular concentration of cyclic adenosine monophosphate. Cilostazol suppresses platelet aggregation and also acts as a direct arterial vasodilator. Cilostazol has been documented in numerous trials to improve exercise capacity in patients with intermittent claudication (97,104–107) and, in a dose of 100 mg twice daily, was shown to be superior to both placebo and pentoxifylline (106).

Cilostazol should be administered to patients with PAD to increase walking distance (Table 4), but should not be given to persons with PAD who also have heart failure. Other contraindications to the use of cilostazol include a creatinine clearance of less than 25 mL/min, a known predisposition for bleeding, or coadministration of CYP3A4 or CYP2C19 inhibitors such as cimetidine, diltiazem, erythromycin, ketoconazole, lansoprazole, omeprazole, and HIV-1 protease inhibitors.

EXERCISE REHABILITATION

Exercise rehabilitation programs have been demonstrated to increase walking distance in persons with intermittent claudication through improvements in peripheral circulation, walking economy, and cardiopulmonary function (108). The optimal exercise program for improving claudication pain distance in persons with PAD uses intermittent walking to near-maximal pain during a program of at least six months (109). Strength training is less effective than treadmill walking (110). The ACC/AHA guidelines recommend a supervised exercise program for patients with intermittent claudication (4) (Table 4).

Supervised exercise training is recommended for a minimum of 30 to 45 minutes in sessions performed at least three times per week for a minimum of 12 weeks (4) and preferably for six months or longer (109). Among persons with PAD, self-directed walking exercise performed at least three times weekly is associated with significantly less functional decline during the subsequent year (111).

FOOT CARE

Persons with PAD must have proper foot care (4,112) (Table 4). They must wear properly fitted shoes. Careless nail clipping or injury from walking barefoot must be avoided. Feet should be washed daily, and the skin kept moist with topical emollients to prevent cracks and fissures, which may have portals for bacterial infection. Fungal infection of the feet must be treated. Socks should be wool or other thick fabric, and padding or shoe inserts...
may be used to prevent pressure sores. When a wound of the foot develops, specialized footgear, including casts, boots, and ankle foot arthoses may be helpful in unweighting the affected area (112).

**LOWER EXTREMITY ANGIOPLASTY AND BYPASS SURGERY**

Table 7 states that the indications for lower extremity percutaneous transluminal angioplasty or bypass surgery are (i) incapacitating claudication in persons interfering with work or lifestyle; (ii) limb salvage in persons with limb-threatening ischemia as manifested by rest pain, nonhealing ulcers, and/or infection or gangrene; and (iii) vasculogenic impotence (113). Percutaneous transluminal angioplasty can be performed if there is a skilled vascular interventionalist and the arterial disease is localized to a vessel segment less than 10 cm in length (113). Compared with percutaneous transluminal angioplasty alone, stenting improves three-year patency by 26% (114). After infrainguinal bypass surgery, oral anticoagulant therapy is preferable in persons with venous grafts, whereas aspirin is preferable in persons with nonvenous grafts (115).

Percutaneous balloon angioplasty and/or stenting is indicated for short-segment stenoses, whereas multisegment disease and occlusions are most effectively treated with surgical revascularization (116). Revascularization of PAD is discussed extensively elsewhere (4,112). In patients presenting with severe limb ischemia caused by infrainguinal disease and who are suitable for either surgery or angioplasty, bypass surgery and balloon angioplasty are associated with similar outcomes in terms of amputation-free survival (117). Patients with intermittent claudication should be considered for revascularization to improve symptoms only in the absence of other disease that would limit exercise improvement such as angina pectoris, heart failure, chronic pulmonary disease, or orthopedic limitations (4).

**AMPUTATION**

Nonrandomized studies have demonstrated that both immediate and long-term survival is higher in patients having revascularization rather than amputation for limb-threatening ischemia (118,119). However, amputation of lower extremities should be performed if tissue loss has progressed beyond the point of salvage, if surgery is too risky, if life expectancy is very low, or if functional limitations diminish the benefit of limb salvage (112).

**ABDOMINAL AORTIC ANEURYSM**

The prevalence of abdominal aortic aneurysm (AAA) increases with advancing age, smoking, hypercholesterolemia, hypertension, male gender, and family history (4,120). The prevalence of an AAA varies from 1.3% for men aged 45 to 54 years to 12.5% for...
men aged 75 to 84 years (4). The prevalence of an AAA varies from 0% for women aged 45 to 54 years to 5.2% for women aged 75 to 84 years (4). Most patients with an AAA are asymptomatic, with their AAA noted on studies performed for other reasons rather than on physical examination. Of 110 men with an AAA, 71% had CAD, 46% had lower extremity PAD, and 27% had cerebrovascular disease (121). The prognosis of an AAA in women is worse than in men (122).

In patients that have evidence of back, abdominal, or groin pain in the presence of a pulsatile abdominal mass, the aorta needs to be evaluated immediately, preferably with computed tomographic scanning. In one study, the mortality rates were 35% for ruptured AAAs, 26% for symptomatic AAAs, and 5% for asymptomatic AAAs undergoing repair (123). In another study, treatment of 96 high-risk patients, mean age 72 years, with an AAA and endovascular stent-graft prosthesis was associated with a 100% survival at 90-day follow-up (124).

The ACC/AHA guidelines recommend that patients with infrarenal or juxtarenal AAAs measuring 5.5 cm or larger should undergo repair to eliminate the risk of rupture (4). Patients with infrarenal or juxtarenal AAAs measuring 4 to 5.4 cm in diameter should be monitored by ultrasound or computed tomographic scans every 6 to 12 months to detect expansion (4).

Patients with AAA should undergo intensive risk factor modification. In one study, use of angiotensin-converting enzyme inhibitors was associated with a reduced risk of ruptured AAA (125). Of 130 patients with AAAs not treated surgically, patients treated with statins (58% of the group) had a significantly lower mortality at 45-month follow-up (5% for statin-treated patients vs. 16% for patients not treated with statins) (126). The size of the AAA was 4.6 cm at baseline versus 4.5 cm at 23-month follow-up in patients treated with statins versus 4.5 cm at baseline and 5.3 cm at 24-month follow-up in patients not treated with statins (126). Use of statins also reduced perioperative mortality in patients undergoing surgical AAA repair (127). In addition, long-term statin use was associated with decreased all-cause mortality and cardiovascular mortality after successful AAA surgery irrespective of clinical risk factors and use of β blockers (128).

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Perioperative Cardiovascular Evaluation and Treatment of Elderly Patients Undergoing Noncardiac Surgery

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Over 30 million patients undergo noncardiac surgery annually in the United States, 4 million of whom are at risk of having coronary artery disease (CAD) on the basis of clinical risk factors. More than 1 million patients have cardiovascular complications postoperatively (1). The health care costs associated with these adverse cardiac outcomes have been estimated to be in excess of $10 billion annually in the United States. With the shifting demographics of the U.S. population, increasingly the elderly represent the majority on whom nearly all surgical procedures are performed.

Cardiovascular complications continue to be a significant etiology of adverse outcome in elderly patients undergoing noncardiac procedures in spite of improvements in surgical and anesthetic techniques and perioperative medical management. These complications are related to a high prevalence of CAD in older patients and to the changes in the cardiovascular system that occur with aging, including a greater prevalence of systolic hypertension (HTN), diastolic left ventricular dysfunction, and blunted responses to the hemodynamic stressors of surgery.

The preoperative evaluation and preparation of the elderly patient undergoing noncardiac surgery represents a unique challenge for the primary care physician, cardiologist, anesthesiologist, and surgeon. The elderly not only have a higher prevalence of cardiovascular disease but also are more likely to need urgent or emergent noncardiac surgical procedures. Therefore, the preoperative evaluation is frequently more complicated and may need to be performed on a more urgent basis. In approaching the elderly surgical patient, the fundamental assumption is that the preoperative evaluation will result in changes in perioperative management.

Since each practitioner has a different perspective with regard to potential perioperative complications, it is important that the various consultants communicate with
each other to reduce an individual patient’s risk. For example, the internist or cardiologist
may be most concerned with the need for preoperative interventions or with assessing the
risks versus benefits of a surgical intervention. From the anesthesiologist’s perspective,
information regarding the patient’s ventricular reserve and cardiac ischemic potential is
critical in determining the optimal intraoperative management. Therefore, communication
is essential in order to achieve the optimal perioperative outcome.

It is important to realize that the preoperative evaluation may also represent the
patient’s initial cardiovascular, and sometimes medical, evaluation. Therefore, strategies
to assess and modify perioperative cardiac risk may also have important long-term
consequences for the patient. To provide the practitioner with an understanding of some
of the issues and concerns for the anesthesiologist and medical caregivers, this chapter
will review those factors that identify the high-risk elderly patient and the preoperative
and perioperative interventions that may modify that risk.

ASSESSMENT OF THE PATIENT BEFORE NONCARDIAC SURGERY

History

Since the highest risk to any elderly patient undergoing noncardiac surgery is related to
cardiovascular complications, a thorough history should focus on cardiovascular risk
factors and symptoms or signs of unstable cardiac disease states such as myocardial
ischemia, congestive heart failure (CHF), valvular heart disease, and significant cardiac
arrhythmias (Table 1). Determining the risk of adverse perioperative cardiac events may
be useful in determining whether the proposed surgery is the ideal approach to achieving
the individual patient’s longer-term goals.

CAD

Symptoms of cardiovascular disease should be carefully determined, especially
characteristics of chest pain, if present. In patients with symptomatic CAD, the
preoperative evaluation may lead to the recognition of an increase in the frequency or
pattern of anginal symptoms.

It is important to realize that certain populations of patients, such as the elderly,
women, or those with diabetes mellitus (DM), may present with more atypical symptoms
of angina pectoris. Often comorbidities may cloud the detection of angina in older
individuals. For example, the patient with lung disease may have dyspnea on exertion that
could be multifactorial, and the debilitated individual may be unable to exercise regularly
enough to detect angina. If unstable angina is present, there is associated high
perioperative risk of myocardial infarction (MI) (2). Even when angina symptoms are
“stable,” there may be a sizeable risk of perioperative myocardial ischemia so that
additional preoperative cardiovascular testing or perioperative monitoring may be useful.
In addition to identifying the severity and stability of CAD, if present, it is also necessary
to know any prior medical or surgical cardiac interventions that have been performed.

CHF

In virtually all studies to date, the presence of symptomatic CHF preoperatively has been
associated with an increased incidence of perioperative cardiac morbidity (2–4). Stabilization
of symptoms of pulmonary congestion is prudent prior to elective surgery. It is important to determine the etiology of the left heart failure since the type of
perioperative monitoring and treatments would be different for such conditions as ischemic or nonischemic cardiomyopathy, systolic or nonsystolic heart failure, or mitral or aortic valvular insufficiency and/or stenosis. Diastolic filling abnormalities are particularly common in older patients and may increase the risk of developing symptomatic heart failure or atrial fibrillation in the perioperative period (5,6).

**MI**

Traditionally, perioperative risk assessment for noncardiac surgery was based upon the time interval between an MI and the surgery. Although many earlier studies demonstrated an increased incidence of reinfarction if surgery is performed within six months of an MI, this time interval may no longer be valid in the current era of thrombolitics, endovascular stenting, and aggressive medical management options after an acute MI (7–9). The American College of Cardiology/American Heart Association (ACC/AHA) Task Force on Perioperative Evaluation of the Cardiac Patient Undergoing Noncardiac Surgery considers those with an acute MI within seven days of the surgical procedure to be at

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**Table 1**  Clinical Predictors of Increased Perioperative Cardiovascular Risk (MI, CHF, Death)

<table>
<thead>
<tr>
<th>Active cardiac conditions</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Unstable coronary syndromes</td>
<td>Unstable or severe angina(^b) (CCS class III or IV)(^c)</td>
</tr>
<tr>
<td>Recent MI(^a)</td>
<td></td>
</tr>
<tr>
<td>Decompensated heart failure (NYHA functional class IV; worsening or new onset HF)</td>
<td></td>
</tr>
<tr>
<td>Significant arrhythmias</td>
<td>High-grade atrioventricular block</td>
</tr>
<tr>
<td></td>
<td>Mobitz II atrioventricular block</td>
</tr>
<tr>
<td></td>
<td>Third-degree atrioventricular heart block</td>
</tr>
<tr>
<td></td>
<td>Symptomatic ventricular arrhythmias</td>
</tr>
<tr>
<td></td>
<td>Supraventricular arrhythmias (including atrial fibrillation) with uncontrolled ventricular rate</td>
</tr>
<tr>
<td></td>
<td>(HR &gt; 100 at rest)</td>
</tr>
<tr>
<td></td>
<td>Symptomatic bradycardia</td>
</tr>
<tr>
<td></td>
<td>Newly recognized VT</td>
</tr>
<tr>
<td>Severe valvular disease</td>
<td>Severe aortic stenosis (mean pressure gradient &gt;40 mmHg, aortic valve area &lt;1.0 cm(^2), or symptomatic)</td>
</tr>
<tr>
<td></td>
<td>Symptomatic mitral stenosis (progressive dyspnea on exertion, exertional presyncope, or heart failure)</td>
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<table>
<thead>
<tr>
<th>Clinical predictors of risk</th>
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<tbody>
<tr>
<td>History of ischemic heart disease</td>
<td></td>
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<tr>
<td>History of compensated or prior heart failure</td>
<td></td>
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<tr>
<td>History of cerebrovascular disease</td>
<td></td>
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<tr>
<td>Diabetes mellitus</td>
<td></td>
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<tr>
<td>Renal insufficiency</td>
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</table>

\(^a\)The American College of Cardiology National Database Library defines recent MI as >7 days but ≤30 days.

\(^b\)May include “stable” angina in patients who are unusually sedentary.


**Abbreviations:** CHF, congestive heart failure; HF, heart failure; HR, heart rate; LOE, level of evidence; MI, myocardial infarction; NYHA, New York Heart Association; VT, ventricular tachycardia; ECG, electrocardiogram.

**Source:** From Fleisher et al. (4b)
highest risk, while those with a prior MI within 7 to 30 days are considered to have an increased, but somewhat lower, risk (10,11).

*Peripheral Arterial Disease*

Peripheral arterial disease has been shown to be associated with CAD in multiple studies since the same risk factors are often responsible for disease in all vascular territories. Hertzer and colleagues studied 1000 consecutive patients scheduled for major vascular surgery and found that approximately 60% of patients had at least one coronary artery with a critical stenosis (12).

*DM*

DM has been shown to be a very strong predictor of perioperative cardiac complications and is common in the elderly and frequently results in noncardiac complications that necessitate urgent or emergent surgery (13). Patients with DM have a greater likelihood of having multivessel CAD, which is often clinically silent. Diabetes that is either longstanding or associated with end-organ dysfunction is felt to place the patient at higher perioperative risk than uncomplicated or newly developed DM. Autonomic neuropathy has recently been found to be the best predictor of silent cardiac ischemia (14). Since patients with DM are at risk for silent MI, a preoperative electrocardiogram (ECG) should be obtained to examine for the presence of prior MI and to serve as a baseline to compare postoperative studies.

*HTN*

Hypertensive patients with left ventricular hypertrophy who undergo noncardiac surgery are at a higher perioperative risk than nonhypertensive patients (15). Individuals with left ventricular hypertrophy and “strain pattern” on ECG may have a greater prevalence of CAD than those without this pattern.

HTN is common and its prevalence increases with age. It is estimated that 24% of the adult population of the United States has HTN and, by age 70, the prevalence increases to more than 60% (16). HTN can result in a more severe form of diastolic dysfunction, which may predispose to CHF. HTN is a known risk factor for cardiovascular, renal, and neurological disease.

Although mild to moderate HTN is not an independent predictor of postoperative cardiac complications, a hypertensive crisis in the postoperative period, defined as a diastolic blood pressure greater than 120 mmHg and clinical evidence of impending or actual end-organ damage, poses a definite risk of MI and cerebrovascular accident (4). Several precipitants of hypertensive crises have been identified, including pheochromocytoma, abrupt clonidine withdrawal prior to surgery, and the use of chronic monoamine oxidase inhibitors with or without sympathomimetic drugs in combination (17).

Chronic HTN may indirectly predispose patients to perioperative myocardial ischemia since CAD is more prevalent in these patients. Even in the absence of CAD, patients with chronic HTN may have episodes of myocardial ischemia, perhaps due to impaired coronary vasodilator reserve and autoregulation, so that higher arterial pressures are required to maintain adequate perfusion of vital organs.

The Study of Perioperative Ischemia Research Group showed that a history of HTN was an independent predictor of postoperative ischemia and increased postoperative mortality (15,18). Patients with a history of HTN had almost twice the risk of developing postoperative myocardial ischemia and almost four times the risk of postoperative death than did patients without HTN in the first 48 hours postoperatively.
The link between systemic HTN and perioperative cardiac complications may relate to an increased risk of silent myocardial ischemia, which has been shown to be a major predictor of postoperative cardiac morbidity (19). In patients who underwent ambulatory ECG ST-segment monitoring to determine the incidence of silent myocardial ischemia before elective noncardiac surgery, at least one episode of ST-segment depression consistent with silent ischemia occurred in 20% of patients (20). Patients with HTN despite antihypertensive therapy were at particularly high risk, with more than a 50% incidence of silent myocardial ischemia. However, continuous ECG ST-segment monitoring may overestimate the incidence of myocardial ischemia in the setting of left ventricular hypertrophy (21).

In patients with significant diastolic HTN (diastolic blood pressure >110 mmHg), the potential benefits of delaying surgery in order to optimize antihypertensive medications should be weighed against the risk of delaying the surgical procedure. A randomized trial of treated hypertensive patients without known CAD who presented the morning of surgery with an elevated diastolic blood pressure was unable to demonstrate any difference in outcome between those who were actively treated with intranasal nifedipine versus those in whom surgery was delayed (22).

Isolated systolic HTN (systolic blood pressure >160 mmHg and diastolic blood pressure <90 mmHg) has been identified as a risk factor for cardiovascular complications in the general population, and treatment has been shown to reduce the future risk of stroke. However, there has been only one study that directly assessed the relationship between perioperative cardiovascular complications and preoperative isolated systolic HTN. In a multicenter study of patients undergoing coronary artery bypass grafting (CABG), the presence of isolated systolic HTN was associated with a 30% increased incidence of cardiovascular complications (23).

In summary, noncardiac surgery should not be postponed or canceled in the otherwise uncomplicated patient with mild to moderate HTN. Antihypertensive medications should be continued perioperatively, and blood pressure should be maintained near preoperative levels to reduce the risk of myocardial ischemia. Continuation of antihypertensive treatment throughout the perioperative period is indicated.

**Physical Examination**

A complete preoperative physical examination is necessary for every patient undergoing noncardiac surgery. Blood pressure and heart rate should be determined in both the supine and standing positions to assess intravascular volume status or autonomic dysfunction. Careful cardiac auscultation should be performed to detect clinically important cardiac findings, including the presence of an S3 gallop suggestive of CHF and murmurs suggestive of significant valvular disease, particularly aortic stenosis. The pulmonary exam and evaluation for jugular venous distention and lower extremity edema can also help determine intravascular volume status and the presence of CHF. Peripheral arterial pulses and bruits may suggest cardiac valvular disease or the presence of occult atherosclerotic disease.

**ESTIMATION OF PERIOPERATIVE CARDIAC RISK**

**Identifying Surgery-Specific Risk**

The surgical procedure influences the extent of the preoperative evaluation required by determining the potential range of changes in perioperative management (Table 2). There is little hard data to define the surgery specific incidence of complications, and the rate
may be very institution dependent. Knowledge of the urgency, type, and anticipated duration of the surgical procedure and the expected blood loss and intravascular volume shifts is necessary to make perioperative management plans.

Surgical procedures that are neither emergent nor associated with significant blood loss are not associated with a high risk of cardiac ischemia. For example, cataract surgery is associated with minimal cardiac stress and exceedingly low cardiac morbidity and mortality rates, even after a recent MI (24). Similarly, outpatient procedures have also been shown to be associated with a low incidence of cardiac morbidity and mortality (25). In such patients, changes in perioperative management are rarely needed unless the patient demonstrates unstable angina or signs or symptoms of CHF.

Eagle et al. published data on the incidence of perioperative MI and mortality by procedure for patients enrolled in the Coronary Artery Surgery Study (CASS) (26). Higher risk procedures for which CABG reduced the risk of noncardiac surgery compared with medical therapy include major vascular, abdominal, thoracic, and orthopedic surgery. Vascular surgery represents a unique group of patients in whom there is extensive evidence regarding preoperative testing and perioperative interventions. Since further determination of cardiac status may alter perioperative care, the benefit of further evaluation and treatment in this population would be expected to be greater than the associated costs or risks of such testing, and has been studied most extensively.

### Identifying Clinical Risk Predictors

Several approaches can be used to estimate perioperative cardiac risk in patients before noncardiac surgery. In early studies, clinical parameters associated with CAD were proven predictors of perioperative morbidity and mortality. In a landmark study in 1977 by Goldman et al., there were nine independent clinical correlates of postoperative cardiac complications in patients undergoing noncardiac surgery. A point system was assigned to each clinical predictor and a cardiac risk index score was calculated to help stratify patients at highest risk perioperatively (3). In 1999, six other independent clinical predictors of risk were included in a Revised Cardiac Risk Index (RCRI): high-risk type of

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**Table 2** Cardiac Riska Stratification for Noncardiac Surgical Procedures

<table>
<thead>
<tr>
<th>Vascular</th>
<th>Aortic and other major vascular</th>
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<tbody>
<tr>
<td></td>
<td>Peripheral vascular</td>
</tr>
<tr>
<td>Intermediate</td>
<td>Reported cardiac risk generally &lt;5%</td>
</tr>
<tr>
<td></td>
<td>Carotid endarterectomy</td>
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<tr>
<td></td>
<td>Head and neck</td>
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<tr>
<td></td>
<td>Intraperitoneal and intrathoracic</td>
</tr>
<tr>
<td></td>
<td>Orthopedic</td>
</tr>
<tr>
<td></td>
<td>Prostate</td>
</tr>
<tr>
<td>Lowb</td>
<td>Reported cardiac risk generally &lt;1%</td>
</tr>
<tr>
<td></td>
<td>Endoscopic procedures</td>
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<tr>
<td></td>
<td>Superficial procedure</td>
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<tr>
<td></td>
<td>Cataract</td>
</tr>
<tr>
<td></td>
<td>Breast</td>
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</tbody>
</table>

aCombined incidence of cardiac death and nonfatal myocardial infarction.
bDo not generally require further preoperative cardiac testing.

*Source*: From Ref. 4b.
surgery, history of ischemic heart disease, history of CHF, history of cerebrovascular disease, preoperative treatment with insulin, and preoperative serum creatinine greater than 2.0 mg/dL (4). It assigns one point each for the presence of six independent risk factors for major cardiac complications in patients having nonemergency surgery. The incidence of major cardiac events in patients with 0, 1, 2, or 3 risk factors was 0.4%, 0.9%, 7%, and 11%, respectively, in the validation cohort. This risk stratification system predicts outcome, but also identifies patients who need additional testing or medical interventions.

Defining Exercise Tolerance

Exercise tolerance is one of the most important determinants of perioperative risk (27). A high exercise tolerance, even in patients with stable angina, is associated with a low perioperative cardiac risk. Estimated energy requirements for various activities can be defined by metabolic equivalent (MET) levels, where 1 MET equals resting energy expenditure of approximately 3.5 mL oxygen/kg/min. Exercise tolerance can be assessed with formal treadmill testing or with a questionnaire that assesses activities of daily living (Table 3). Perioperative cardiac risk is increased in patients unable to achieve 4 METs during normal daily activities (27). Estimation of MET capacity can be done accurately and simply by asking specific questions during the preoperative interview that assess functional capacity (Table 3) or by using simple questionnaires that have been developed for this purpose (28,29).

For example, if a patient can walk a mile without developing chest discomfort or unusual shortness of breath, then the probability of severe CAD is small. On the other hand, if a patient develops chest pain during minimal exertion, then the probability of extensive CAD is high as is the perioperative risk. In one study of outpatients referred for evaluation before major noncardiac procedures, patients were asked to estimate the number of blocks they could walk and flights of stairs they could climb without experiencing cardiac symptoms (27). Patients who could not walk four blocks and climb two flights of stairs were considered to have poor exercise tolerance and were found to have more perioperative cardiovascular complications. The likelihood of a serious

### Table 3  Estimated Energy Requirement for Various Activities

<table>
<thead>
<tr>
<th>METs</th>
<th>Activities</th>
</tr>
</thead>
</table>
| 1 MET | Can you take care of yourself?  
| | Eat, dress, or use the toilet?  
| | Walk indoors around the house?  
| | Walk a block or two on level ground at 2-3 mph or 3.2–4.8 km/h?  
| | Do light work around the house like dusting or washing dishes? |
| 4 METs | Climb a flight of stairs or walk up a hill?  
| | Walk on level ground at 4 mph or 6.4 km/h?  
| | Run a short distance?  
| | Do heavy work around the house like scrubbing floors or lifting, or moving heavy furniture?  
| | Participate in moderate recreational activities like golf, bowling, dancing, doubles tennis, or throwing a baseball or football?  
| >10 METs | Participate in strenuous sports like swimming, singles tennis, football, basketball, or skiing? |

**Abbreviation:** MET, metabolic equivalent.

**Source:** From Ref. 11.
complication occurring was inversely related to the number of blocks that could be walked or flights of stairs that could be climbed.

**APPROACH TO THE PATIENT**

In 1996, an ACC/AHA Task Force developed Guidelines for Perioperative Cardiovascular Evaluation for Noncardiac Surgery (10). These guidelines were developed to provide a framework for cardiac risk stratification for those undergoing noncardiac surgery, acknowledging the lack of prospective, randomized trials in this area. The guidelines were updated in 2002 (11). These guidelines assess clinical risk predictors (Table 1), type of surgery (Table 2), and exercise tolerance (Table 3) to be performed in an algorithm model to assist in decision making for further preoperative cardiac testing. In 2007, the Guidelines were updated again and the algorithm was revised (Fig. 1), and the RCRI was utilized to stratify the need for further testing (4b). First, the clinician must evaluate the urgency of the surgery and the appropriateness of a formal preoperative assessment. Next, determine if the patient has undergone a previous revascularization procedure or coronary evaluation. Those patients with unstable coronary syndromes should be identified and appropriate treatment instituted. Finally, the decision to undertake further testing depends upon the interaction of the clinical risk factors, surgery-specific risk, and functional capacity. For patients at intermediate clinical risk, both the exercise tolerance and the extent of the surgery are taken into account with regard to the need for further testing. No preoperative cardiovascular testing should be performed if the results will not change perioperative management. Therefore, the best approach to the algorithm is that pathways that lead to the operating room do not need testing. For those pathways that may suggest testing, the recommendation is not for mandatory testing, but simply identification of a group that may benefit if the results of testing will influence care. Since coronary revascularization has not been shown to be beneficial in patients undergoing major vascular surgery with small to moderate areas at risk for ischemia, the need for testing in any asymptomatic patient with moderate exercise tolerance is negligible. This is further supported by the lack of efficacy of a testing protocol demonstrated by our group in a small randomized trial of 99 patients who were at low or intermediate cardiovascular risk undergoing major vascular surgery and underwent either no testing or preoperative diagnostic testing with interventions based upon the results of the test (30). Importantly, this was a highly functional ambulatory group that was seen in a preoperative cardiology clinic and was begun on optimal medical therapy. In this highly select group of patients, the overall rate of morbid cardiac events was very low, and we were unable to demonstrate any difference in outcome between those tested and the no-testing group. There were no patients in this cohort in whom preoperative cardiac imaging demonstrated a sufficiently large area at risk to warrant coronary revascularization, further supporting the contention that preoperative testing in highly functional vascular surgery patients may not be indicated.

**DIAGNOSTIC TESTING**

The sensitivity, specificity, and accuracy of the stress-testing modality and its cost must be considered along with the prevalence of CAD in the population. A positive stress test for myocardial ischemia may not have the same meaning in a population with a low prevalence of CAD as in a population with a high prevalence of CAD. As described above, no preoperative cardiovascular testing should be performed if the results will not change perioperative management.
Figure 1  Algorithm to evaluate patients undergoing noncardiac surgery. Source: From Ref. 4b.
Some studies raise questions about the usefulness of preoperative noninvasive stress testing before noncardiac surgery, while other studies consider it useful in specific populations (11). In general, the negative predictive values of the specific stress testing modalities studied in these patient populations are high. Therefore, in a patient with a negative stress test for myocardial ischemia, the risk of a perioperative cardiac event is relatively low. On the other hand, the positive predictive values of available stress tests are consistently low, so that a patient with evidence of stress-induced myocardial ischemia often still has a good perioperative outcome. This may be explained by the fact that an acute MI is often caused by the rupture of a non-flow-limiting, unstable coronary artery plaque (31). Stress testing detects flow-limiting coronary artery stenoses (>50% to 70% arterial lumen narrowing), but cannot detect stenoses that are non-flow limiting.

Resting Electrocardiography

A routine ECG before noncardiac surgery solely on the basis of age is no longer recommended based on the literature (32). Therefore, the clinical history of the patient and surgical risk should be utilized to determine the need for an immediate preoperative electrocardiogram. A preoperative resting 12-lead ECG is recommended for patients with known coronary heart disease, peripheral arterial disease, or cerebrovascular disease who are undergoing intermediate-risk surgical procedures. A preoperative resting 12-lead ECG is reasonable in persons with no clinical risk factors undergoing vascular surgical procedures. It has been estimated that up to 30% of MIs are silent and only detected on routine ECG, especially in diabetics and patients with HTN. The baseline ECG has limited applicability in the assessment of myocardial ischemia but may be useful to detect significant conduction disturbances and arrhythmias. ECG abnormalities may not always lead to delay of a noncardiac surgical procedure but may lead to increased vigilance by the anesthesiologist intraoperatively.

High-grade atrioventricular block, symptomatic ventricular arrhythmias in the presence of underlying heart disease, and supraventricular arrhythmias with uncontrolled ventricular rate are considered high-risk clinical predictors by the ACC/AHA Guidelines (11). Pathological Q waves are considered intermediate-risk clinical predictors. The presence of left ventricular hypertrophy, left bundle branch block, ST-segment abnormalities, and rhythm other than sinus are considered minor risk predictors.

Despite the absence of evidence to suggest that a 12-lead ECG is required in all patients immediately prior to noncardiac surgery, the availability of an old ECG may be useful for comparison. Frequently, patients may have subtle ECG changes pre-, intra- or postoperatively.

Assessment of Left Ventricular Function

In general, an assessment of baseline left ventricular function should be reserved for those with unexplained cardiopulmonary symptoms. This can be accomplished using echocardiography, radionuclide angiography, and/or contrast ventriculography. Most commonly, however, echocardiography is used when assessment of left ventricular function is felt to be warranted. Left ventricular ejection fraction has been correlated with short- and long-term prognosis in multiple studies in patients undergoing noncardiac surgery; in general, the lower the ejection fraction, the greater the perioperative risk (11). Some recent studies have found that left ventricular systolic dysfunction does not predict cardiac complications after vascular surgery (33). Importantly, Halm and colleagues were unable to demonstrate that preoperative echocardiographic information added to clinical risk factors for risk stratification (34).
The ACC/AHA Task Force Guidelines recommend that preoperative assessment of left ventricular systolic function prior to noncardiac surgery should be limited to patients with current or poorly controlled CHF but not as a routine test in patients without prior CHF (4b). Among patients with a history of CHF and with dyspnea of unknown etiology, the indications are less clear.

Continuous ECG ST-Segment Monitoring

Multiple studies have demonstrated the association between major cardiac events and perioperative ST-segment changes detected by continuous ECG monitoring. The duration of perioperative ST-segment changes has been shown to be the strongest predictor of poor outcome (35,36). Continuous ST-segment monitoring is typically used during the intraoperative period for high-risk patients, although ST-segment changes may not always indicate myocardial ischemia (37).

The value of continuous ECG ST-segment monitoring for all patients is unclear. In one study, preoperative myocardial ischemia detected by this method was found to be the most significant independent predictor of adverse postoperative cardiac events (38). The absence of ischemia was associated with a very high negative predictive value. Cardiac events occurred more often in patients with higher postoperative heart rates or if patients had a history of diabetes, clinical manifestations of CAD, or were older than 70 years. Intraoperative ECG ST-segment changes consistent with ischemia, on the other hand, were a significant, but relatively weak, predictor of postoperative events, especially in patients with a low prevalence of CAD. Since it is unclear whether early detection of ST-segment changes will lead to improved treatment and patient outcome, the utility of continuous ECG ST-segment monitoring is unclear, and it should not be used routinely in the perioperative period. In fact, overly aggressive treatment of ST-segment changes of nonischemic origin could theoretically increase morbidity, costs, or both.

Noninvasive Cardiac Stress Testing

The ultimate goal of a preoperative cardiac stress test is to identify patients with myocardial ischemia in whom further cardiac interventions would significantly lower perioperative cardiac risks. In patients undergoing major vascular surgery, which carries the highest perioperative cardiac risk, noninvasive cardiac testing has been found to be helpful for cardiac risk stratification (11,39). Unfortunately, there are few prospective, randomized studies that establish the value of preoperative testing and clearly demonstrate that therapy based on these test results affects perioperative outcomes.

An important aspect of cardiac stress testing relies on Bayes’ theorem, which states that the correct interpretation of the results of noninvasive stress testing requires estimating the pretest probability of CAD in the patient being studied. False-positive stress test results are more common in those in whom CAD is unlikely to be present and false-negative results are more common in those with a high likelihood of CAD. Therefore, determining the probability of CAD in a specific patient will often guide decision making even before a stress test is considered.

A limited number of prospective studies have investigated the predictive value of noninvasive cardiac stress tests in determining the risk of postoperative cardiac events. The positive predictive values of all stress testing modalities are poor (10% to 20%), so that a patient with evidence of myocardial ischemia often will not have a postoperative cardiac event even though the estimated cardiac risk is high. On the other hand, negative predictive values of most cardiac stress testing modalities are high (95% to 100%), so that...
patients without evidence of ischemia are at the lowest risk for an adverse perioperative outcome. The likelihood of an adverse cardiac event after noncardiac surgery, even in patients with evidence of CAD, is less than 10% (64,65).

If noninvasive cardiac stress testing is recommended, the optimal test for the preoperative evaluation for noncardiac surgery in ambulatory patients is the exercise treadmill ECG to determine functional capacity and to detect myocardial ischemia (11). In patients with baseline ECG abnormalities or in those who are unable to ambulate, nuclear scintigraphic or echocardiographic imaging should be used, depending on the expertise of the interpreters.

**Exercise ECG Cardiac Stress Testing**

In patients with a normal baseline ECG without a prior history of CAD, the exercise ECG response is abnormal in up to 25% of cases. In those with a prior history of MI or an abnormal resting ECG, the exercise ECG response can be abnormal in up to 50% of cases (40). If an ischemic response occurs at a low cardiac workload, the positive predictive value of the test for determining a high cardiac risk is further increased. Reduced exercise duration and exercise-induced ST-segment depression, in most but not all, studies have been shown to correlate with an increased likelihood of postoperative cardiac events.

In the general population, the usefulness of treadmill ECG test without imaging is somewhat limited. The mean sensitivity and specificity are 68% and 77% for detection of single-vessel disease, 81% and 66% for detection of multivessel disease, and 86% and 53% for detection of three-vessel or left main CAD. The older age of patients undergoing noncardiac and vascular surgery reduces the sensitivity and prognostic utility of exercise stress testing in this group (41). Often these patients will have a submaximal treadmill exercise study, not being able to achieve their maximum predicted heart rate due to medical therapy, such as β-blocker use, or to comorbid states, which can limit the results. Indeed, when considering the utility of preoperative noninvasive cardiac stress testing in an elderly individual undergoing noncardiac surgery, clinicians must ask whether the study sample on which recommendations are based is relevant to the individual patient being cared for.

Patients with intermediate- to high-risk clinical profiles who reach a cardiac workload of more than 5 METs or a heart rate greater than 75% to 85% of maximum age predicted with a non-ischemic ECG response are at low risk for postoperative cardiac events (41). A patient’s performance on a treadmill or bicycle ergometer may also be predictive of postoperative cardiac outcomes (42). The level at which ischemia is evident on the exercise ECG can be used to estimate an “ischemic threshold” for a patient to guide perioperative medical management. This may support further intensification of perioperative medical therapy in high-risk patients, which may impact on perioperative cardiovascular events.

**Pharmacological Cardiac Stress Testing**

Pharmacological stress testing has been advocated for preoperative cardiac risk assessment for patients in whom exercise tolerance is limited. Often, these patients may not exercise sufficiently during daily life to provoke symptoms of myocardial ischemia or CHF. Pharmacological stress tests with echocardiographic or nuclear scintigraphic imaging have been studied extensively in preoperative cardiac risk assessment for noncardiac, and especially vascular, surgery and will be briefly reviewed here.

An abnormal preoperative dipyridamole-thallium scintigraphy scan has been shown to be a sensitive predictor of postoperative cardiac events (11,39). Pooled data, though, show that the positive predictive value for adverse cardiac outcomes is low, ranging from 36% to 45%. The negative predictive value, on the other hand, is high (up to 97%). In several studies,
the presence of a fixed defect was shown to have no predictive value for adverse postoperative cardiac outcomes, although, in two studies, there was a higher risk compared to patients with no ischemic defect. Preoperative dipyridamole-thallium scintigraphy was found to be superior to the clinical assessment alone for the determination of cardiac risk in early studies.

More recent studies support the use of preoperative dipyridamole-thallium scintigraphy, in combination with clinical parameters, to identify patients at high risk for adverse cardiac outcomes after noncardiac surgery. In the initial study by Eagle et al. of patients undergoing vascular surgery, an abnormal preoperative dipyridamole-thallium scan was the most significant predictor of postoperative ischemic events. The likelihood of an ischemic event was 7% if the scan was negative and 45% if it revealed ischemia (43). Clinical predictors of postoperative events were pathological Q waves on ECG and evidence of redistribution defects. Patients with no clinical predictors were at low perioperative cardiac risk, and their perioperative outcomes were not affected by the results of preoperative stress testing. In a second study by Eagle in a similar patient population, five clinical variables were predictive of postoperative cardiac events: age over 70 years, Q waves on baseline ECG, history of angina, ventricular ectopic activity requiring therapy, and diabetes (44). Dipyridamole-thallium scintigraphy was found to be most useful in further stratifying patients considered at intermediate clinical risk (one or two clinical variables). In this group, the presence of a redistribution defect was associated with a 30% event rate compared to a 3% event rate in those without a thallium redistribution defect. In more than 50% of cases, the dipyridamole-thallium stress test did not add incremental information to the preoperative assessment after clinical variables were evaluated. Many studies have found that dipyridamole-thallium scintigraphy scans with a large number and size of redistribution defects, presence of left ventricular dilatation after stress, or pulmonary radiotracer uptake are predictive of a higher postoperative cardiac risk (39).

The accuracy of dipyridamole-thallium scintigraphy in the preoperative evaluation of patients before noncardiac surgery has been challenged. In one study, intraoperative myocardial ischemia was assessed using continuous ECG monitoring and transesophageal echocardiography in patients undergoing vascular surgery (45). All had dipyridamole-thallium scintigraphy preoperatively, and all treating physicians were blinded to the results. There was a 5% incidence of adverse postoperative cardiac outcomes, with no association between redistribution defects and adverse cardiac outcomes. The sensitivity and specificity of thallium scintigraphy for all adverse outcomes were low (40–54% and 65–71%, respectively). The positive predictive value was low (27–47%) and the negative predictive value relatively high (61–82%). It was proposed that routine use of dipyridamole-thallium scans for preoperative screening of patients before vascular surgery may not be warranted. A study by Baron using SPECT, which has been found to have an increased sensitivity for the detection of CAD, confirmed these findings (46). Initial data using technetium 99m sestamibi, a newer myocardial perfusion tracer, indicate that it has the same diagnostic accuracy as thallium 201 for the detection of myocardial ischemia.

There are few studies that evaluate the long-term postoperative outcomes of patients with abnormal dipyridamole-thallium scans. In one study, an abnormal dipyridamole-thallium scan was associated with a significantly increased risk of cardiac death in the perioperative period and in late follow-up in comparison to those with a normal scan (47). A reversible defect was the only predictor of death or MI during late follow-up and was associated with a twofold greater risk of a cardiac event than if the defect was fixed. The number of perfusion defects, a history of angina, and the presence of chest pain during the study were independent predictors of perioperative cardiac events. Fleisher et al. utilized criteria from the Thrombolysis in Myocardial Infarction IIIB (TIMI-IIIB) trials for quantification of dipyridamole-thallium results (48). They reported a significantly increased
long-term risk only in the subset of patients with high-risk thallium markers, including increased lung uptake and multiple segments with reversible defects.

Dobutamine stress echocardiography (DSE) involves the identification of new or worsening myocardial wall motion abnormalities (WMAs) using two-dimensional echocardiography during infusion of intravenous dobutamine. This technique has been shown to have the same accuracy as dipyridamole-thallium scintigraphy for the detection of CAD. More recently, DSE has been found to be useful for the assessment of preoperative cardiac risk among patients undergoing noncardiac surgery (39). The estimated low positive predictive values (17–43%) and high negative predictive values (93–100%) are similar to those for dipyridamole-thallium. There are several advantages to DSE compared with dipyridamole-thallium scintigraphy. DSE can also assess valvular abnormalities, the cost of DSE is significantly lower, there is no radiation exposure, and the duration of the study is significantly shorter.

Several studies have assessed the value of DSE in preoperative risk assessment. The results of DSE add significantly to the clinical risk assessment of patients undergoing major vascular surgery, particularly in patients with intermediate clinical risk (49). As with other forms of preoperative risk assessment, however, DSE has a relatively low positive predictive value and many patients with abnormal test results do not have adverse postoperative cardiac events.

Presently, there are few studies that report long-term cardiac outcomes after noncardiac surgery among patients with abnormal preoperative DSE. In one study, patients were followed for up to two years after major vascular surgery (67). There were two cardiac events (3%) among patients with negative DSE. Among patients with positive DSE, 68% subsequently underwent coronary revascularization before the noncardiac surgery was performed. There were no perioperative events in the group of patients with positive DSE who underwent coronary revascularization before noncardiac surgery. By contrast, 40% of those with positive DSE who did not undergo coronary revascularization had perioperative adverse cardiac outcomes. In this study, DSE predicted perioperative and long-term outcome among patients undergoing major vascular surgery, with a high negative predictive value. In a second study, patients undergoing major vascular surgery were evaluated by clinical parameters and results of DSE and followed for an average of 19 months postoperatively (97). The presence of extensive dobutamine-induced WMAs and a previous history of MI independently predicted late cardiac events, increasing risk up to sixfold.

Comparison of the different tests
A meta-analysis of 15 studies that compared dipyridamole-thallium scintigraphy and DSE for risk stratification before vascular surgery in intermediate-risk patients found that the prognostic value of both techniques is comparable, but that the accuracy varies with CAD prevalence (50). Beattie et al. performed a meta-analysis of 68 studies and 10,278 patients who had noncardiac surgery from 1985 to 2003 (Table 4) (39). The likelihood ratio of a positive DSE in predicting a cardiac complication was twice that of dipyridamole thallium imaging (DTI), 4.09 (95% CI, 3.21–6.56) versus 1.83 (95% CI, 1.59–2.10). There was no difference in the ability of either test to predict complications in patients with moderate to large perfusion defects or regions of WMAs. The likelihood of false negatives was also higher for DTI than for DSE, likelihood ratio 0.44 (95% CI, 0.36–0.54) versus 0.23 (95% CI, 0.17–0.32). In the seven studies directly comparing these two tests, no statistically significant difference in likelihood ratios could be found for either positive or negative tests. Over a third of the complications found in their meta-analysis occurred in patients with a negative stress test. In summary, given the large overlap in predictive
value between the tests, the best choice of test is left to the individual center since local expertise can influence the predictive value of the tests.

**CORONARY ANGIOGRAPHY AND REVASCULARIZATION BEFORE NONCARDIAC SURGERY**

**Coronary Angiography**

An abnormal noninvasive study in the preoperative period may lead to coronary angiography and revascularization, to changes in anesthetic technique, to utilization of expensive resources such as intensive care units, or to aggressive treatment of hemodynamic fluctuations. Historically, the use of coronary angiography as a screening procedure before elective peripheral vascular surgical procedures was advocated due to the high perioperative mortality associated with the high prevalence of CAD in this patient group (12). Many argue that using coronary angiography as a preoperative screening tool is too costly and places patients at further risk due to the cumulative risks of these procedures, especially in the elderly with significant comorbid diseases. This has led to increased interest in preoperative noninvasive cardiac stress testing to assist in risk-stratifying patients before elective noncardiac surgery and to the increased use of perioperative β-blocker therapy, particularly in high-risk patients based on clinical parameters.

The present indications for coronary angiography in the preoperative evaluation before noncardiac surgery are adapted from the ACC/AHA Guidelines for coronary angiography in the general population (51). Coronary angiography should be considered in patients with unstable symptoms of angina pectoris, recent MI, or large areas of myocardium at risk on noninvasive stress tests if coronary revascularization would be considered.

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**Table 4** Meta-analysis Comparison of SE to TI as a Preoperative Screening Tool

<table>
<thead>
<tr>
<th>Variable analyzed</th>
<th>Stress echocardiography</th>
<th>Stress scintigraphy</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Likelihood ratio (95% CI)</td>
<td>Likelihood ratio (95% CI)</td>
</tr>
<tr>
<td>All studies</td>
<td>4.09 (3.21–6.56)</td>
<td>1.83 (1.59–2.10)</td>
</tr>
<tr>
<td>Vascular studies only</td>
<td>4.75 (3.44–6.56)</td>
<td>1.83 (1.57–2.13)</td>
</tr>
<tr>
<td>Studies with blinding procedures only</td>
<td>5.52 (3.45–8.85)</td>
<td>1.73 (1.11–2.71)</td>
</tr>
<tr>
<td>Studies completed after 1995</td>
<td>3.75 (2.89–4.87)</td>
<td>1.79 (1.45–2.21)</td>
</tr>
<tr>
<td>Studies with routine screening for MI</td>
<td>4.11 (2.85–5.93)</td>
<td>1.60 (1.22–2.08)</td>
</tr>
<tr>
<td>Direct comparisons of SE to TI only</td>
<td>3.78 (2.10–6.79)</td>
<td>1.73 (0.96–3.11)</td>
</tr>
<tr>
<td>Quantitative studies (comparison of ROC)a</td>
<td>0.80 (0.75–0.84)</td>
<td>0.75 (0.70–0.80)</td>
</tr>
<tr>
<td>Surgical selection (proportion sent to angiography)b</td>
<td>12.0 (8.7–16.2)</td>
<td>29.1 (18.5–39.6)</td>
</tr>
<tr>
<td>Proportion revascularizedb</td>
<td>57.5 (34.0–81.0)</td>
<td>29.0 (18.0–30.1)</td>
</tr>
</tbody>
</table>

*aExpressed as receiver operating characteristic curve (95% CI).

*bExpressed as percentage of patients (95% CI).

**Abbreviations:** MI, myocardial infarction; TI, thallium imaging; SE, stress echocardiography; ROC, receiver operating characteristic.

*Source:* From Ref. 39.
Coronary Revascularization (Table 5)

Although earlier, nonrandomized, retrospective studies have suggested that high-risk patients undergoing noncardiac surgery might derive benefit from preoperative coronary artery revascularization (26), more recent randomized trials indicate that coronary revascularization does not improve perioperative outcomes even in high-risk patients, and the rates of perioperative adverse events are significantly increased with surgery performed within six weeks following stent placement. Eagle and colleagues reported a long-term analysis of patients in the CASS registry who received medical or surgical therapy for CAD and who subsequently underwent 3368 noncardiac operations over the next 10 years (26). The rate of perioperative MI and death was stratified by the type of surgical procedure. Specifically, low-risk surgeries such as skin, breast, urological, and minor orthopedic procedures were associated with a total morbidity and mortality of less than 1%, and prior revascularization did not affect outcome. Intermediate-risk surgery, such as abdominal or thoracic procedures or carotid endarterectomy, was associated with a combined morbidity and mortality of 1% to 5%, with a small but significant improvement in outcome among patients who underwent prior coronary revascularization. The most significant improvement in outcome was noted among patients undergoing major vascular surgery who underwent prior coronary revascularization. Therefore, in this nonrandomized study, CABG prior to noncardiac surgery was beneficial in selected subgroups.

The Coronary Artery Revascularization Prophylaxis (CARP) trial showed that coronary artery revascularization before elective vascular surgery did not significantly alter long-term outcome (52). In this trial, 510 patients at increased risk for perioperative cardiac complications were randomized to undergo either coronary artery revascularization or no revascularization before elective major vascular surgery. Among the patients assigned to undergo revascularization, percutaneous coronary intervention (PCI) was performed in 59% and CABG in 41%. There was no difference between groups in either postoperative MI or in mortality at 2.7 years after randomization. Of note, however, only a minority of patients in this trial had three-vessel CAD. Poldermans et al. studied 770 patients undergoing major vascular surgery and at intermediate cardiac risk, defined as the presence of one or two cardiac risk factors (age >70 years, angina, history of MI, a history of or compensated CHF, diabetes, creatinine >2.0 mg/dL, or previous transient ischemic attack or cerebrovascular accident) (53). Patients were randomized to either undergo further risk stratification with DSE or proceed to surgery. Patients with three or more risk factors were excluded from the study and considered for further risk stratification. All patients received preoperative bisoprolol that was continued after surgery, with a targeted heart rate of 60 to 65 bpm. Physicians were not blinded to the results of DSE, and heart rate was kept below the ischemic threshold with tight perioperative β-blocker control. Of the 34 patients who were considered for revascularization because of extensive ischemia on DSE, 12 underwent revascularization (10 PCI and 2 CABG), with complete revascularization in only 6. The 30-day incidence of cardiac death and nonfatal MI was similar in both groups (1.8% in the no testing group vs. 2.3% in the tested group). Poldermans et al. published results from the Dutch Echocardiographic Cardiac Risk Evaluation Applying Stress Echo (DECREASE)-V pilot study, which randomized 101 patients, the majority of whom had three-vessel or left main CAD, to undergo coronary revascularization or no revascularization before major vascular surgery (54). In this population of patients with severe coronary disease, extensive stress-induced ischemia on DSE, and an average age of approximately 70 years, coronary revascularization did not affect the composite end point of death or MI at either 30 days or one year.
## Table 5  Strategies to Reduce Cardiac Risk of Noncardiac Surgery

<table>
<thead>
<tr>
<th>Category</th>
<th>Patient selection</th>
<th>Specific therapy</th>
<th>Quality of supporting data</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Medical therapy</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>β-Blockers</td>
<td>Patients already receiving them; patients with CAD or at high cardiac risk</td>
<td>Continue prior regimen; ideally begin treatment days to weeks preoperative (e.g., atenolol 25–50 mg q.d. or metoprolol intravenously, titrating to achieve heart rate ≤ 60 bpm)</td>
<td>Most convincing data exist for patients undergoing vascular surgery with known CAD and provicable ischemia on stress test. No data to support acute administration for patients without known CAD</td>
</tr>
<tr>
<td></td>
<td>undergoing vascular surgery or patients with CAD undergoing intermediate- or high-risk procedures</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Statins</td>
<td>Patients already receiving statins</td>
<td>Continue prior administration and initiate as soon as possible</td>
<td>Cohort study demonstrating increased morbidity if not reinitated before 4th postoperative day</td>
</tr>
<tr>
<td>α-2-Adrenergic agonists</td>
<td>Patients with existing CAD undergoing vascular surgery</td>
<td>Clonidine 0.2 mg orally and a clonidine patch.</td>
<td>α-2-Adrenergic agonists may have a role in reducing cardiac complications of noncardiac surgery, but their place in perioperative management is not yet clear</td>
</tr>
<tr>
<td>Calcium channel blockers</td>
<td>Patients requiring calcium channel blockers to control angina and/or provicable ischemia</td>
<td>Continue prior regimen</td>
<td>May reduce myocardial ischemia (see text)</td>
</tr>
<tr>
<td>Nitrates</td>
<td>Patients previously requiring nitrates to control angina and/or provicable ischemia; patients developing perioperative ischemia without hypovolemia</td>
<td>Continue prior regimen; institution of intravenous delivery</td>
<td>Limited trial data; no convincing prophylactic value</td>
</tr>
<tr>
<td>PCI</td>
<td>Patients with coronary artery disease undergoing noncardiac surgery</td>
<td>PCI in patients with coronary artery disease, even with extensive ischemia on cardiac stress testing, does not appear to improve perioperative outcomes in noncardiac surgery</td>
<td>Recent randomized studies call into question the notion that preoperative coronary revascularization improves outcome, even in high-risk patients. Whether these results will be confirmed in larger randomized studies is unclear, as is the role of preoperative coronary revascularization in patients with unstable angina pectoris</td>
</tr>
<tr>
<td>Coronary artery bypass surgery</td>
<td>Patients with coronary artery disease undergoing noncardiac surgery</td>
<td>Coronary revascularization in patients with coronary artery disease, even with extensive ischemia on cardiac stress testing, does not appear to improve perioperative outcomes in noncardiac surgery</td>
<td>There are a relatively small number of patients who underwent CABG in the recent randomized studies that examine the role of preoperative coronary revascularization before noncardiac surgery. Larger, randomized studies that include more patients undergoing CABG are needed</td>
</tr>
</tbody>
</table>

*Abbreviations: CAD, coronary artery disease; bpm, beats per minute; PCI, percutaneous coronary intervention; CABG, coronary artery bypass grafting.*
CABG for three-vessel CAD may be beneficial. When Ward and colleagues reanalyzed the CARP data, they reported fewer perioperative MIs after the vascular operation in CABG patients (6.6%) than in PCI patients (16.8%), despite more diseased vessels in the CABG group (55). Landesberg and colleagues reported improved long-term survival in patients with intermediate clinical risk factors who had stress testing and coronary revascularization (56). Therefore, revascularization by CABG for selected patients with extensive disease may show benefit.

**PCI**

The benefit of PCI before noncardiac surgery has also been examined in several cohort studies. Posner and colleagues utilized an administrative data set of patients who underwent PCI and noncardiac surgery in Washington State (57). They matched patients with coronary disease undergoing noncardiac surgery with and without prior PCI and looked at cardiac complications. In this nonrandomized design, they noted a significantly lower rate of 30-day cardiac complications in patients who underwent PCI at least 90 days before the noncardiac surgery. Importantly, PCI within 90 days of noncardiac surgery did not improve outcome. Although the explanation for these results is unknown, they may support the notion that PCI performed “to get the patient through surgery” may not improve perioperative outcome, since cardiac complications may not occur in patients with stable and/or asymptomatic coronary stenosis, and PCI may actually destabilize coronary plaques which become manifest in the days or weeks after noncardiac surgery.

PCI using coronary stenting poses several special issues. Kaluza and colleagues reported on the outcome in 40 patients who underwent prophylactic coronary stent placement less than six weeks before major noncardiac surgery requiring general anesthesia (58). There were 7 MIs, 11 major bleeding episodes, and 8 deaths. All deaths and MIs, as well as 8 of 11 bleeding episodes, occurred in patients subjected to surgery fewer than 14 days after stenting. Four patients expired after undergoing surgery one day after stenting. Wilson and colleagues reported on 207 patients who underwent noncardiac surgery within two months of stent placement (59). Eight patients died or suffered an MI, all of whom were among the 168 patients undergoing surgery six weeks after stent placement. Vincenzi et al. studied 103 patients and reported that the risk of suffering a perioperative cardiac event was 2.11-fold greater in patients with recent stents (<35 days before surgery) compared with PCI more than 90 days before surgery (60). Leibowitz et al. studied a total of 216 consecutive patients who had a PCI within three months of noncardiac surgery (112 balloon angioplasty and 94 stent) (61). A total of 26 patients (12%) died, 13 in the stent group (14%) and 13 in the balloon angioplasty group (11%), a nonsignificant difference. The incidence of acute MI and death within six months were not significantly different (7% and 14% in the stent group and 6% and 11% in the PTCA group, respectively). Significantly, more events occurred in the two groups when noncardiac surgery was performed within two weeks of PCI. On the basis of the accumulating data, elective noncardiac surgery after PCI, with or without stent placement, should be delayed for four to six weeks.

Drug-eluting stents (DES) may represent an even greater problem during the perioperative period on the basis of case reports. Nasser et al. described two patients with in-stent thrombosis occurring 4 and 21 months after implantation of sirolimus-eluting stents (62). If dual antiplatelet therapy is interrupted before noncardiac surgery in an effort to limit perioperative bleeding, there may be an increased risk of major adverse cardiac events (63, 64).

In February of 2007, the ACC/AHA in conjunction with the Society for Cardiovascular Angiography and Interventions, American College of Surgeons, the
American Dental Association, and the American College of Physicians, published an advisory statement regarding the premature discontinuation of dual antiplatelet therapy after coronary stent placement (65). It recommended that strong consideration be given to the placement of bare metal stents (BMS) in patients likely to undergo surgery within 12 months and that elective surgery be deferred for one year in patients with DES who would be at high risk for perioperative bleeding if dual antiplatelet therapy were continued. For patients with a DES, who need surgical procedures within 12 months of stent placement, and in whom discontinuation of thienopyridine therapy is absolutely necessary, it is advised that aspirin be continued and thienopyridine therapy restarted as soon as possible. There is limited evidence regarding how soon after either DES or BMS placement surgery can safely be conducted if dual therapy is continued. A certain period of time is required for the stent to endothelialize, and there is also concern regarding smooth muscle proliferation in response to the endothelial injury during placement.

PERIOPERATIVE INTERVENTIONS TO REDUCE RISK (TABLE 5)

Intra-Aortic Balloon Counterpulsation

Among patients with unstable angina or severe CAD, placement of an intra-aortic balloon counterpulsation device has been used before induction of anesthesia in patients considered high-risk for noncardiac surgical procedures. In several small case series, perioperative morbidity and mortality were low (66). In clinical practice, however, intra-aortic balloon counterpulsation is seldom used before noncardiac surgery except in the most unstable patients with ongoing myocardial ischemia and a need for an emergency surgical procedure.

Perioperative CHF

It is critical to optimize the medical management of CHF, both systolic and diastolic, before an elective noncardiac surgical procedure. For patients with left ventricular systolic dysfunction, this often involves the use of diuretics, angiotensin-converting enzyme inhibitors, and \( \beta \) blockers. These medications can alter hemodynamic and metabolic parameters that may impact on perioperative cardiac risk. Patients at risk for CHF postoperatively are those with a history of arrhythmia and DM and those undergoing prolonged surgical procedures. Patients who develop isolated CHF postoperatively have a better long-term prognosis than those in whom a postoperative myocardial ischemic event occurs. (67)

\( \beta \) Blockers

Several studies in the late 1970s indicated that \( \beta \)-blocker therapy could be safely continued preoperatively, often resulting in a reduction in the incidence of perioperative myocardial ischemia (68). These studies, and the concern for \( \beta \)-blocker withdrawal–induced tachycardia, HTN, and myocardial ischemia, led to recommendations to continue \( \beta \)-blocker therapy preoperatively (69).

By decreasing adrenergic stimulation of the heart, \( \beta \) blockers may reduce the incidence of perioperative arrhythmias and myocardial ischemia. In a study of patients with mild to moderate HTN undergoing general anesthesia, the use of a single low-dose oral \( \beta \) blocker produced a 13-fold reduction in the incidence of intraoperative myocardial ischemia by ECG (70). Among patients not receiving \( \beta \) blocker therapy, ischemia was detected in 28%. All episodes occurred either during tracheal intubation or emergence
from anesthesia. In those treated with β-blocker therapy, only 2.2% had evidence of myocardial ischemia. Those who received β blockers more frequently developed bradycardia, had a greater fall in mean arterial pressure during premedication, and had less of a pressor response during tracheal intubation and emergence from anesthesia. The prophylactic use of β-blocker therapy in patients at high risk of postoperative cardiac complications appears to be safe and effective.

The first well-designed randomized, placebo-controlled study in high-risk non-cardiac surgical patients involved the perioperative use of atenolol, which was administered beginning two days preoperatively and continued for seven days postoperatively (71,72). A significantly lower incidence of perioperative ischemia and improved event-free six-month survival was observed in the atenolol group. No difference in perioperative MI or cardiac death was noted between groups. Of note, several risk factors and medications were not equally distributed in the two groups, with the placebo group having a higher risk profile. In a study of the perioperative use of bisoprolol in elective major vascular surgery, this medication was administered at least seven days preoperatively, titrated to achieve a resting heart rate of 60 bpm or less, and continued postoperatively for 30 days (73). Of note, the study was confined to patients with one or more clinical markers of cardiac risk (prior MI, DM, angina pectoris, CHF, age over 70, or poor functional status), and with myocardial ischemia on DSE. Patients with large zones of myocardial ischemia were excluded from the trial. Bisoprolol led to an approximate 80% reduction in perioperative MI or cardiac death. The efficacy of bisoprolol in the highest risk group, those who would be considered for coronary revascularization or modification or cancellation of the surgical procedure, is unknown. However, the event rate in the placebo group (nearly 40%) suggests that all but the highest risk patients were enrolled in the trial.

The same data were then reevaluated with respect to clinical factors, DSE results, and β-blocker usage (13). A clinical risk score was calculated by assigning one point for each of the following characteristics: age 70 years or older, current angina, MI, CHF, prior cerebrovascular events, DM, and renal failure. Importantly, DSE was performed only in patients with a significant number of risk factors. Those patients who demonstrated new WMAs had higher event rates than those without new WMAs, for the same clinical risk score. When the risk of death or MI was stratified by perioperative β-blocker usage, there was no significant improvement in those without any of the prior risk factors. In those with fewer than three clinical risk factors, the use of β blockers was associated with a lower rate of cardiac events (0.8% vs. 2.3%), and β-blocker therapy was very effective in reducing cardiac events in those with limited stress-induced ischemia on DSE (33% vs. 2.8%). By contrast, β-blocker therapy had no effect in patients with more extensive stress-induced ischemia on DSE.

Lindenauer et al. published a retrospective cohort study conducted by searching a database used by 329 participating hospitals for quality assessment (74). A total of 119,454 patients were given β blockers perioperatively, defined as the administration of β blockers within the first or second day of hospitalization. There was no effect on in-hospital mortality for the entire cohort (2.3% vs. 2.4%). For patients with an RCRI score of 3 or higher, β blockers were protective; patients with an RCRI score of 1 had no mortality benefit. For those with an RCRI of 0, in-hospital mortality increased with the use of perioperative β blockade.

The subsequent literature was less encouraging. The Perioperative Beta-Blockade for Patients Undergoing Infra-renal Vascular Surgery (POBBLE) trial enrolled 103 patients who were randomized to placebo or metoprolol, typically the night before surgery, and for seven days postoperatively (75). Patients were excluded if they had a
history of MI within two years of surgery or angina with a positive stress test. There was no statistically significant difference in 30-day cardiovascular morbidity and mortality. Symptomatic bradycardia and hypotension were higher in the study group with an increased requirement for inotropic support. The Metoprolol after Vascular Surgery (MaVS) trial studied 496 patients who had major vascular surgery, of which 297 patients had an RCRI of 1 (1 point given for undergoing vascular surgery) and 47 patients had an RCRI of 3 or higher (76). Patients were randomized to placebo or metoprolol two hours preoperatively and then postoperatively for up to five days. In patients with an RCRI of lower than 2, there was no statistically significant difference in 30-day cardiovascular outcome. In those with a RCRI of 3 or higher, the incidence of 30-day complications was higher in the metoprolol group, 7 of 19 versus 4 of 28, although the number of events was too small for significance. There was a significantly higher incidence of need for treatment of bradycardia and hypotension in the metoprolol group. The Diabetic Postoperative Mortality and Morbidity (DIPOM) trial included 921 diabetic patients older than 40 years who required major nonvascular surgery lasting more than one hour. Patients were excluded if they had indications for outpatient β-blocker treatment, which was not otherwise specified. Metoprolol or placebo was given the night before surgery and continued for seven days or until hospital discharge. There was no statistically significant difference in cardiovascular outcome over the 18-month follow-up (77).

There are several considerations regarding the optimal protocol for perioperative β-blockade. Feringa et al. studied 272 vascular surgery patients and their β-blocker doses (78). In multivariate analysis, higher β-blocker doses were significantly associated with a lower incidence of myocardial ischemia, troponin T release, and long-term mortality. Higher heart rate during ECG monitoring was significantly associated with an increased incidence of myocardial ischemia, troponin T release, and long-term mortality. The authors suggested that controlling heart rate to lower than 70 bpm was ideal. There is also some evidence to suggest that long-acting agents are superior because of a lower incidence of plasma level troughs. A longer preoperative administration period allows better titration with less under- and overdosing. When Redelmeier et al. reviewed 37,151 patients who had received atenolol or metoprolol before surgery, they found that 1038 patients experienced an MI or died. The rate of death or MI was significantly lower for patients given atenolol than for those given metoprolol (2.5% vs. 3.2%, p < 0.001). The decreased risk with atenolol persisted after adjustment for measured demographic, medical, and surgical factors. The authors concluded that the metoprolol group did not have as low a perioperative cardiac risk as patients given atenolol, because of possible acute withdrawal after missed metoprolol doses. This supported the use of longer-acting agents with tight heart rate control (79).

A number of meta-analyses have examined the evidence supporting perioperative β-blocker therapy. Although these meta-analyses generally demonstrate that β-blockers reduce some perioperative events, evidence of an effect on perioperative mortality is inconsistent. Several meta-analyses have found evidence to support a role of perioperative β-blocker therapy in the reduction of perioperative myocardial ischemia and in composite outcomes of cardiac death and nonfatal MI with or without the inclusion of nonfatal cardiac arrest (80–83). Some have found that β-blockers reduce perioperative MI or cardiac mortality, but another meta-analysis failed to find an effect of β-blockers on perioperative myocardial infarction or overall mortality (83). One meta-analysis found that perioperative β-blockers did not show statistically significant beneficial effects on any of the individual outcomes (total mortality, cardiovascular mortality, nonfatal myocardial infarction, nonfatal cardiac arrest, nonfatal stroke, or CHF at 30 days) (80). This review found that β-blockers did increase the risk of bradycardia and hypotension requiring treatment, both side effects to which geriatric patients may be particularly predisposed.
The recent ACC/AHA 2006 Guideline Update on Perioperative Cardiovascular Evaluation for Noncardiac Surgery that focused on perioperative β-blocker therapy gave a Class I recommendation (conditions for which there is evidence for and/or general agreement that the procedure or treatment is beneficial, useful, and effective) for the use of perioperative β-blockers in patients already receiving them and in patients undergoing vascular surgery at high cardiac risk because of ischemia on cardiac stress testing (84) (Fig. 2). A class IIa recommendation (weight of evidence or opinion is in favor of the usefulness or efficacy of the treatment) was given for perioperative β-blocker use in patients with CAD or who are at high risk and are undergoing vascular surgery or undergoing intermediate- or high-risk procedures. A class IIa recommendation was also given to perioperative β-blockers for patients with CAD who are undergoing vascular surgery.

Since publication of the Guidelines the POISE trial has been presented at the American Heart Association Annual Meeting. In a randomized trial of metoprolol CR versus placebo begun the day of surgery and continued for 30 days, metoprolol was associated with a lower incidence of the primary endpoint of cardiovascular death, MI or cardiac arrest (Hazard ratio [HR] 0.83, 95% CI 0.70–0.99). Importantly, total mortality was increased in the metoprolol group (3.13 vs. 2.33, P = 0.004). Therefore, the risks of new acute administration at beta-blockers may outweigh the benefits.

Statins

Most recently, perioperative statins have been shown to improve cardiac outcome. In a case-controlled study, Poldermans and colleagues were able to show that statin therapy was associated with reduced mortality after vascular surgery, even in the subset of patients on β-blocker therapy (85). Durazzo and colleagues published a randomized trial of 200 vascular surgery patients in which statins were started an average of 30 days prior to vascular surgery (86). A significant reduction in cardiovascular complications was demonstrated using this protocol. Hindler and colleagues conducted a meta-analysis to evaluate the overall effect of preoperative statin therapy on postoperative outcomes (87). Preoperative statin therapy was associated with 59% reduction in the risk of mortality (1.7% vs. 6.1%; p = 0.0001) after vascular surgery. When including noncardiac surgery, a 44% reduction in mortality (2.2% vs. 3.2%; p = 0.0001) was observed. Le Manach and colleagues studied patients undergoing infrarenal aortic surgery and compared those on chronic statin therapy who had their statin
continued immediately postoperatively versus those who had a period in which it was discontinued (88). They demonstrated that postoperative statin withdrawal (>4 days) was an independent predictor of postoperative myonecrosis (odds ratio 2.9, 95% CI, 1.6–5.5) (88). It is therefore critical that statins be continued perioperatively.

Nitroglycerin

Continuous intravenous infusions of nitroglycerin, a venodilator, are most useful for the management of perioperative HTN. The postoperative patient with CHF and/or ischemic heart disease may also benefit from its use. Nitroglycerin may also reduce preload and improve myocardial oxygen supply. Prolonged use should be avoided due to potential tachyphylaxis.

Nitroglycerin has been a mainstay of anti-ischemic therapy, but its value during the perioperative period is controversial. Two randomized clinical trials have focused on high-risk noncardiac surgery patients. Coriat et al. studied a cohort of patients undergoing carotid endarterectomy using a high-dose narcotic anesthetic technique (89). They demonstrated a significantly reduced incidence of myocardial ischemia with 1.0 μg/kg/min of nitroglycerin compared to 0.5 μg/kg/min; no patients sustained a perioperative MI. Another study compared nitroglycerin at 1.0 μg/kg/min to placebo in high-risk patients undergoing noncardiac surgery and demonstrated no difference in perioperative myocardial ischemia or infarction (90). Many of the effects of nitroglycerin are mimicked by the anesthetic agents, minimizing some of the potential beneficial effects of nitroglycerin and potentially leading to more profound hypotension. Therefore, the evidence does not support the routine prophylactic use of this agent.

α-2-Adrenergic Agonists

α-2-adrenergic agonists have received a great deal of attention as adjuvants to anesthetic management. Clonidine stimulates central α-2-adrenergic receptors and thereby decreases sympathetic nervous outflow to the vasculature, producing vasodilation and lowering blood pressure. Clonidine may be useful for the management of postoperative HTN. It is available for oral and transdermal use and should be continued in the patient taking clonidine preoperatively in order to avoid a withdrawal syndrome. Clonidine should not be used in patients with high-grade atrioventricular conduction disturbances.

Clonidine has been shown to significantly decrease the incidence of intra-operative ischemia compared with placebo in patients undergoing noncardiac surgery (91). In patients undergoing elective vascular surgery, clonidine reduced the incidence of perioperative myocardial ischemia, and there were fewer nonfatal MIs among patients treated with clonidine compared to those who received placebo (92). In one prospective, randomized, double-blinded, clinical trial, 190 patients with, or at risk for, CAD received clonidine or placebo in the perioperative period. Clonidine significantly decreased the incidence of perioperative myocardial ischemia and significantly reduced postoperative mortality for up to two years (93). A meta-analysis of 23 randomized trials comparing preoperative, intraoperative, or postoperative (within the first 48 hours) administration of α-2-adrenergic agonists with controls found that α-2-adrenergic agonists significantly reduced ischemia and mortality after noncardiac surgery (94). α-2-adrenergic agonists also significantly reduced mortality and myocardial infarction during vascular surgery (94). Although these results suggest that α-2-adrenergic agonists may have a role in reducing cardiac complications of noncardiac surgery, their place in perioperative management is not yet clear.

Calcium Channel Antagonists

Calcium channel blockers may be useful in the management of postoperative HTN, but some may produce reflex tachycardia; this is particularly true of the dihydropyridine
compounds like nifedipine. In one systematic review of 11 studies of calcium channel blockers before noncardiac surgery, these drugs were found to significantly reduce the development of myocardial ischemia and supraventricular tachycardia (95). Use of calcium channel blockers was associated with a trend toward reduced death and MI, and in post hoc analyses, they significantly reduced the combined end points of death and MI. The majority of these benefits were attributable to diltiazem. Further studies of calcium channel blockers, and perhaps of diltiazem in particular, appear warranted in the perioperative setting.

Cardiac Devices

Temporary or Permanent Pacemaker Placement Prior to Surgery
In general, perioperative temporary pacemaker placement is indicated for high-grade conduction abnormalities and marked bradycardia with associated symptoms. In cases where symptoms are not present, easy access to temporary transvenous pacemaker equipment in the operating room is advised. Recommendations for temporary or permanent pacemaker implantation in patients undergoing noncardiac surgery are the same as those for elective pacemaker implantations for patients not undergoing surgical procedures. As with all invasive procedures, the risk of temporary pacemaker placement must be considered.

Management of Permanent Pacemakers
Over 460,000 individuals in the United States have permanent pacemakers, 85% of whom are over the age of 65. It is important that the type of pacemaker implanted is known in order to guide perioperative management if issues arise. Major pacemaker manufacturers provide technical support for particular devices, as does the cardiologist who implanted the device, if available. A conservative recommendation is that a pacemaker be interrogated at least two months prior to an elective procedure. Indications for use of perioperative pacemakers and management of preexisting devices are generally based on expert opinion. No established evidence-based guidelines are available. In general, noncardiac surgery should be delayed for 48 hours after permanent pacemaker implantation, if possible, to minimize the risk of acute dislodgment of the pacemaker leads.

The American Society of Anesthesiologists has issued recommendations for the perioperative care of patients with cardiac rhythm management devices (96). Based on these recommendations and those reviewed elsewhere, once it has been determined that a patient has a cardiac rhythm management device (i.e., a permanent pacemaker or an implantable cardioverter defibrillator) based on the history, physical examination, and review of chest radiographs and ECGs, the type of device must be determined (97). This can generally be done by contacting the patient’s cardiologist or the clinic responsible for regular device checks. Patients also typically have a card or other form that indicates the manufacturer of the device. It is important to determine the extent to which the patient is pacemaker dependent. If the patient is known to have complete heart block with an inadequate ventricular rate or severe symptomatic bradycardia, he or she should be considered dependent on the device to sustain an adequate heart rhythm. If the pacemaker was implanted after atrioventricular node ablation (for example, to control a rapid ventricular response to atrial fibrillation), the patient should also be considered device dependent. This information can also be obtained from the patient’s cardiologist or the clinic responsible for regular device checks. Preoperative evaluation involves several steps, which are reviewed in the American Society of Anesthesiologists Task Force practice advisory cited earlier (96). These include determining whether electromagnetic
interference is likely to occur during the planned surgical procedure; determining whether reprogramming pacing function to asynchronous mode or disabling rate responsive function is advantageous given the likelihood of such interference; and suspending antitachyarrhythmia functions that may be present.

Electrocautery may interfere with pacemakers by causing oversensing in patients with unipolar and, rarely, bipolar systems. In this case, it is recommended that the electrocautery electrode be kept at least 4 to 6 inches away from the pacemaker to minimize electrical interference. A pacemaker could be programmed to a fixed-rate mode to avoid reprogramming problems. Preoperatively, in cases of emergent surgery or situations in which the pacemaker cannot be interrogated, a magnet should be placed over the pacemaker and an ECG recorded to evaluate the backup mode and function of the pacemaker. A programming device specific for the interrogation of the pacemaker being used should be available in the operating room when the potential for electrocautery interference is high, the use of defibrillation or cardioversion is expected, or when there has been a noted change in the function and pacing mode of the pacemaker. Pacing thresholds may be decreased because of hypoxia and myocardial ischemia and may be raised because of hyperkalemia and acid/base disturbances. Endocarditis prophylaxis for patients with permanent pacemakers before noncardiac surgery is not indicated in most cases (98).

Management of Automatic Implantable Cardiac Defibrillators

Management of the automatic implantable cardiac defibrillator (AICD) in the perioperative setting is based on the recommendations outlined above. The consultant should know the manufacturer of the device. In general, the device should be inactivated and appropriate resuscitation equipment should be available in the operating room. If the electrophysiologist who implanted the device is available, he or she could provide expert assistance. Also, the technical support provided by the major AICD manufacturers may provide specific recommendations. The AICD can be left in the inactivated mode until the patient is transferred to an unmonitored hospital bed. Endocarditis prophylaxis for patients with an AICD is not generally recommended (98).

SPECIFIC MEDICAL CONDITIONS

Hypertrophic Cardiomyopathy

It is estimated that the prevalence of hypertrophic cardiomyopathy in the adult population is 0.2% (99). Patients with this condition typically have marked degrees of left ventricular hypertrophy, reduced ventricular compliance, hyperdynamic left ventricular systolic function and systolic anterior motion of the mitral valve leaflet, with or without a dynamic pressure gradient in the subaortic area. It is important to identify this condition preoperatively since there may be increased risk of hemodynamic compromise in the perioperative period. Atrial fibrillation is also more common in patients with hypertrophic cardiomyopathy. The overall prevalence of this arrhythmia among patients with hypertrophic cardiomyopathy is greater than 20% and the occurrence of atrial fibrillation increases with age.

Patients with hypertrophic cardiomyopathy may report a family history of cardiomyopathy or of sudden, unexpected death at a young age. A history of cardiac symptoms should be carefully determined, especially chest pain, dyspnea, and syncope. The systolic murmur of hypertrophic cardiomyopathy is quite characteristic, and dynamic auscultation during passive leg elevation or while having the patient change from the
standing to the squatting position typically demonstrates a decrease in the intensity of the murmur. Doppler echocardiography is definitive in the identification of this condition.

Hreybe, et al. searched the National Hospital Discharge Survey database from 1996 to 2002 for patients with a diagnosis of hypertrophic cardiomyopathy who had undergone noncardiac surgery (100). They matched 227 patients with hypertrophic cardiomyopathy with 554 controls by age, gender, and year of surgery. The in-hospital incidence of death or MI was higher in patients with hypertrophic cardiomyopathy than in controls. Even after controlling for age, gender, race, presence of HTN, DM, history of CAD, history of CHF, atrial fibrillation, and ventricular arrhythmias in a multivariate binary logistic regression model, the presence of hypertrophic cardiomyopathy significantly increased the odds of death by 61% and almost tripled the odds of the combined end point of death or MI. It had been recommended that spinal anesthesia be avoided in these patients because it can decrease systemic vascular resistance and increase venous capacitance; although the evidence is very weak, regional anesthesia has been used successfully in these patients (101,102).

As a result of the pathophysiology of hypertrophic cardiomyopathy, patients with this condition are particularly susceptible to factors that alter left ventricular filling, such as diminished intravascular volume, alterations in systemic vascular resistance, and increases in heart rate. Special care should be taken to maintain adequate intravascular volume, minimize pain and anxiety, and avoid treatment with catecholamines. If hypotension does occur in a patient with hypertrophic cardiomyopathy, hydration is indicated, as is consideration of treatment with β blockers, either with or without administration of an α-1-adrenergic agonist like phenylephrine. Drugs like dopamine, dobutamine, and nitroglycerin should be avoided.

Intensive care unit monitoring, which may include pulmonary artery catheter monitoring, may be useful postoperatively to limit periods of hypotension and avoid volume depletion, although its usefulness has not been established.

Diastolic Dysfunction

The hypertensive heart is typically characterized by concentric left ventricular hypertrophy, normal or above-normal systolic function, and diastolic dysfunction. In the elderly patient with marked concentric left ventricular hypertrophy and small end-systolic chamber sizes, diastolic dysfunction can lead to pulmonary congestion. This population may be particularly sensitive to factors that affect diastolic filling of the left ventricle, such as increased heart rate, atrial fibrillation, or volume depletion. Identifying chronically hypertensive patients with diastolic dysfunction with reliable echocardiography parameters could guide optimal perioperative fluid and blood pressure management.

Echocardiography should be considered in the patient with chronic HTN and a history of exertional or stress-induced dyspnea, particularly if there is evidence of left ventricular hypertrophy on the ECG. Exercise may produce a suboptimal increase or even a decrease in left ventricular ejection fraction in these individuals, apparently in some cases due to impaired diastolic filling. The hemodynamic response to the stress of anesthesia and surgery might be expected to produce a similar response.

Increased sympathetic nervous system activity producing increases in blood pressure and heart rate may occur as the patient emerges from anesthesia. This response may compromise diastolic filling, so it is critical to assess volume status at this time. In certain patients, this may be extremely difficult without continuous invasive hemodynamic monitoring. While a pulmonary artery catheter cannot be routinely recommended, it may provide important information in special circumstances in which patients are hemodynamically unstable.
Valvular Heart Disease

Valvular heart disease is frequently encountered in elderly patients undergoing surgical procedures. The known prevalence of valvular heart disease might be greater today than in the past due to the more widespread use of echocardiography. Patients with mitral or aortic valvular disease are more likely than others to experience perioperative cardiac events. The ACC/AHA Guidelines indicate that severe valvular disease is a major clinical predictor of increased perioperative cardiovascular risk (11). A very early study of only 23 patients considered severe aortic stenosis, defined by physical examination criteria and by other supportive data when available, to be the most significant valvular lesion (3). A later study in which all patients underwent echocardiography showed that selected patients with moderate-to-severe aortic stenosis can undergo noncardiac surgical procedures at a relatively low risk (103). Patients with mitral regurgitation, mitral stenosis, or aortic regurgitation may have an increased risk of developing new or worsening CHF but do not appear to have an increased risk of perioperative cardiac mortality. All of these valvular conditions are reviewed below.

Two of the main issues in the perioperative management of patients with valvular heart disease are antibiotic prophylaxis against infective endocarditis and the management of anticoagulation in the perioperative period in patients with prosthetic heart valves. Recently, the AHA updated their recommendations for the prevention of infective endocarditis (98). The new recommendations represent “substantive changes” from the prior guidelines. Specifically, the new guidelines only recommend antibiotic prophylaxis before dental procedures “that involve manipulation of gingival tissue or the periapical region of teeth or perforation of the oral mucosa” for certain patients considered to be at highest risk of acquiring endocarditis. These patients include those who have a prosthetic heart valve, those who have had a previous episode of infective endocarditis, individuals with certain types of congenital heart disease, who have received a heart transplant, and who have developed cardiac valvulopathy. Moreover, the new AHA guidelines do not recommend administration of antibiotics solely to prevent endocarditis for patients who undergo a genitourinary (GU) or gastrointestinal (GI) tract procedure, although they may be considered under special circumstances (i.e., when there is an established GU or GI tract infection or in a patient receiving antibiotic therapy to prevent wound infection or sepsis associated with a GU or GI tract procedure). The reader should refer to the AHA document for a more thorough discussion of this subject (98).

Mitral Stenosis

The major concerns in the patient with mitral stenosis undergoing noncardiac surgery are: (1) maintaining hemodynamic stability; (2) decreasing the incidence of perioperative arrhythmia such as atrial fibrillation; and (3) prevention of infective endocarditis.

Increases in heart rate reduce left ventricular filling across the stenotic mitral valve and increase the transmitral pressure gradient. Patients with mitral stenosis can become symptomatic with tachycardia, such as induced during the perioperative period. β Blockers may be used to reduce heart rate in an attempt to optimize hemodynamic conditions. Antiarrhythmic agents may be considered to prevent the development of atrial fibrillation since this arrhythmia is particularly likely in these patients. Unrecognized mitral stenosis must be included in the differential diagnosis of the patient who develops acute pulmonary edema in the perioperative period. Mitral valve balloon valvuloplasty is often a reasonable alternative to mitral valve surgery in patients who require intervention for symptoms due to significant mitral stenosis before proceeding to
noncardiac surgery. Results have been favorable, especially in younger patients with mitral stenosis, but without severe mitral valve leaflet thickening or significant subvalvular calcification (104).

**Mitral Regurgitation**

Mitral regurgitation is more common than mitral stenosis. When the regurgitation is severe, left ventricular function is often reduced, left atrial and pulmonary vascular pressures are elevated, and atrial fibrillation may be present. Mitral regurgitation is less likely than mitral stenosis to cause abrupt clinical deterioration in the perioperative period unless there are associated valvular lesions, such as aortic stenosis or left ventricular dysfunction. In one study, mitral regurgitation was a significant univariate correlate of cardiac perioperative morbidity and postoperative mortality, but the predictive value did not persist after controlling for other criteria of heart disease in a multivariate analysis (105).

**Aortic Stenosis**

The patient with suspected aortic stenosis merits further evaluation prior to noncardiac surgery, since those with severe aortic stenosis are considered to be at high risk (3). Despite advances in anesthetic technique and perioperative management, patients with severe aortic stenosis still have a relatively high perioperative risk when undergoing noncardiac surgery. This risk appears to be related to the severity of aortic stenosis, to whether CAD is also present, and to the type (and risk) of the surgical procedure (106). Aortic stenosis is more common in men, is particularly a condition of the elderly, and usually results from degenerative calcific aortic valve disease or calcification of a congenitally bicuspid valve. Although cardiac output may increase normally with exercise in asymptomatic patients with aortic stenosis, stroke volume may decrease. Thus, a normal hemodynamic response to exercise or to the stress of the perioperative period may be critically dependent on an increase in heart rate. In symptomatic and more severe aortic stenosis, the cardiac output may not increase normally with increasing metabolic demand. Patients with moderate-to-severe valvular aortic stenosis typically develop concentric left ventricular hypertrophy and diastolic left ventricular dysfunction.

Asymptomatic patients with significant aortic stenosis may be considered for valve replacement prior to noncardiac surgery unless this is not feasible due to the urgent nature of the procedure or due to unacceptably high risk (107). The ACC/AHA Guidelines recommend that elective noncardiac surgery be postponed or canceled until aortic valve replacement is performed in patients with severe, symptomatic aortic stenosis, although there are reports that selected patients with aortic stenosis, even when severe, may be able to safely undergo noncardiac surgery with meticulous perioperative monitoring and care (103,108).

Cardiac stress testing may be indicated prior to noncardiac surgery in patients with aortic stenosis since it may be difficult to distinguish whether chest pain or dyspnea is due to significant aortic stenosis or myocardial ischemia. The safety of exercise stress testing in patients with aortic stenosis has been questioned since exercise-induced cardiac events, particularly effort syncope, have been described. The American College of Physicians (ACP)/ACC/AHA Task Force Statement on exercise testing lists severe aortic stenosis as a general contraindication to exercise testing (40). Nevertheless, some studies have indicated that patients with varying degrees of valvular aortic stenosis may safely undergo treadmill stress testing. One study of a small number of patients suggests that adenosine nuclear scintigraphy may be safely performed in patients with moderate-to-severe aortic stenosis (109). Dobutamine echocardiography has also been safely performed in patients with severe aortic stenosis (110).
General anesthesia may be preferable to spinal anesthesia in asymptomatic patients with mild aortic stenosis since the hemodynamic effects of spinal anesthesia may be undesirable. Patients with moderate-to-severe aortic stenosis may also benefit from close postoperative hemodynamic monitoring in an intensive care unit.

The long-term outcome of patients who undergo percutaneous aortic balloon valvuloplasty for significant aortic stenosis is generally poor primarily due to restenosis (111–113). This procedure may be used for palliation prior to noncardiac surgery (114). Aortic valvuloplasty may acutely reduce the severity of aortic stenosis, but the procedure has significant risk. Fatal cardiac arrest complicating the procedure has been reported in approximately 3% of patients (111). In one report, 4.9% of patients died within the first 24 hours after valvuloplasty and 7.5% died during the hospitalization (115). Acute catastrophic complications including ventricular perforation, acute severe aortic regurgitation, cerebrovascular accident, and limb amputation have been reported in approximately 6% of patients (116). In a study of elderly patients, Doppler echocardiography showed that while the aortic valve mean gradient decreased significantly after the procedure, it increased to near preprocedure levels approximately six months later (112).

Aortic Regurgitation

Patients with chronic aortic regurgitation may have marked degrees of left ventricular hypertrophy and dilatation and eventually develop systolic dysfunction. As is true of patients with mitral regurgitation, those with isolated chronic aortic regurgitation typically do not deteriorate abruptly in the perioperative period.

Prosthetic Heart Valves

More than 60,000 cardiac valve replacements are performed each year in the United States. Issues important in the perioperative period for those with prosthetic valves include the management of chronic anticoagulation therapy, reducing the risk of infective endocarditis, preventing valve thrombosis, and identifying valve-related hemolysis (98).

There are two major types of mechanical prosthetic heart valves, the caged-ball and the tilting-disk valves. The St. Jude valve, a type of tilting-disk valve, is the most commonly used prosthetic valve in the world. While mechanical prosthetic valves have greater durability than bioprosthetic valves, they are more thrombogenic. The risk of valve thrombosis is greatest in patients with caged-ball prosthetic valves (Starr–Edwards). Single-tilting-disk prosthetic valves (Bjork–Shiley, Medtronic-Hall, and Omnicarbon) have an intermediate risk of valve thrombosis, and bileaflet tilting-disk prostheses (St. Jude, Carbomedics, Edwards Duromedics) pose the lowest risk of the mechanical prosthetic valves. The possibility of prosthetic valve dysfunction may be suggested by new cardiac symptoms and abnormal auscultatory findings on physical examination. Mechanical prosthetic valves may be evaluated with cinefluoroscopy. Echocardiography or cardiac catheterization may be warranted in some situations.

The management of chronic warfarin anticoagulation in the perioperative period is of major importance in patients with mechanical prosthetic heart valves. The risk of temporarily discontinuing anticoagulation must be weighed against the benefit of a reduced risk of perioperative bleeding for all patients on chronic anticoagulation, especially those with prosthetic heart valves. In general, the incidence of thromboembolism in patients with valvular heart disease depends on the valve involved, the type of prosthetic heart valve, the existence of concomitant heart disease, the presence of left atrial enlargement, and whether atrial fibrillation is present.
For most elective noncardiac surgical procedures in which blood loss is anticipated, it is generally recommended that patients with prosthetic valves who are taking warfarin have this therapy stopped three to five days before surgery (117). Some have recommended briefly reducing the level of warfarin anticoagulation to the low therapeutic or subtherapeutic range for minimally invasive surgical procedures and then resuming the usual warfarin dose after the procedure, but this recommendation can only be made with information about the potential for blood loss, if the surgery does not go as planned (118).

Those patients with the greatest risk of thromboembolism should be therapeutically anticoagulated with intravenous heparin during the three to five preoperative days in which warfarin is discontinued; the heparin infusion should be continued until several hours before surgery (117,119). The use of subcutaneous low molecular weight heparin for thromboprophylaxis in patients with mechanical prosthetic heart valves who must have oral anticoagulation temporarily interrupted for a surgical procedure (i.e., for “bridging” therapy) is highly controversial. This is, in part, related to reports of adverse outcomes in pregnant women with mechanical prosthetic heart valves. Use of low molecular weight heparin as bridging therapy in nonpregnant patients, though, is also controversial. In one recent review of this topic, Seshadri, et al. concluded that based on the available data, low molecular weight heparin may be a safe and effective agent in patients with mechanical prosthetic heart valves (120). However, there is still much debate on the safety of low molecular weight heparin in this situation and, as the authors note, “future large-scale, randomized trials are warranted.” Whatever form of heparin is used as bridging therapy, it is recommended that warfarin should be restarted as soon as possible following surgery, and that heparin should be resumed and continued until oral anticoagulation is in the therapeutic range.

INTRAOPERATIVE MANAGEMENT

Anesthetic Agents

There are many different approaches to the anesthetic care and intraoperative monitoring of the patient with CAD, depending on the integration of patient- and surgery-specific factors. The type of anesthesia used was not found to be an independent predictor of 30-day mortality in a multivariate analysis (121).

There are three classes of anesthetics: general, regional, and local/sedation or monitored anesthetic care (MAC), defined as local anesthesia administration by the surgeon, both with and without sedation. Outcome studies specifically addressing anesthetic technique in high-risk patients will be discussed after a review of the pharmacology of specific agents.

General Anesthesia

General anesthesia can best be defined as a state including unconsciousness, amnesia, analgesia, immobility, and attenuation of autonomic responses to noxious stimulation, which can be achieved with inhalational agents, intravenous agents, or their combination. General anesthesia can be achieved with or without an endotracheal tube. Traditionally, laryngoscopy and intubation were thought to be the time of greatest stress and risk for myocardial ischemia, but recent studies suggest that extubation is the time of greatest risk (122).

There are five approved inhalational anesthetic agents in the United States, all of which have reversible myocardial depressant effects and decrease myocardial oxygen demand, depending on their concentration and effects on systemic vascular resistance and
baroreceptor responsiveness (Table 6). Overall, there appears to be no one best inhalation anesthetic for patients with CAD. The available agents are briefly reviewed below.

Halothane is rarely used because of its slow onset and offset and its association with hepatitis. Enflurane moderately decreases systemic vascular resistance and depresses baroreceptor function, while isoflurane is a more potent vasodilator and has minimal effects on baroreceptor function. Isoflurane has become the most widely used anesthetic, even for patients with CAD. Several large-scale studies of these inhalational agents in patients undergoing CABG have not demonstrated any increased incidence of myocardial ischemia or infarction (123,124).

Two newer inhalation agents, desflurane and sevoflurane, are available. Desflurane has the fastest onset and is commonly used in the outpatient setting, although it has been shown to be associated with airway irritability leading to tachycardia. In a large-scale study comparing a narcotic-based anesthetic with desflurane, the desflurane group had a significantly higher incidence of myocardial ischemia (125). By including narcotics with desflurane, this tachycardia can be avoided. Sevoflurane is the newest approved agent for use in the United States.

There are theoretical advantages to the use of inhalational anesthetics in patients with CAD. Several investigative groups have demonstrated in vitro and in animal models that these agents possess protective effects on the myocardium similar to ischemic preconditioning (126,127). This favorable effect on myocardial oxygen demand would serve to offset the theoretical effects of coronary steal in patients with chronic coronary occlusion.

### Table 6  Clinical Qualities of Inhaled Anesthetics

<table>
<thead>
<tr>
<th>Agent</th>
<th>Advantages</th>
<th>Disadvantages</th>
</tr>
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| Nitrous oxide | Rapid uptake and elimination  
Minimal respiratory depression  
Minimal circulatory depression  
Odorless, nonpungent | Supports combustion  
Expansion of closed air spaces  
Inactivates vitamin B₁₂  
Lack of anesthetic potency |
| Halothane  | Potent anesthetic  
Nonpungent  
Stable heart rate | Requires preservatives  
Slow uptakes and elimination  
Undergoes biotransformation  
Idiosyncratic hepatic necrosis  
Sensitization to catecholamine-induced cardiac dysrhythmias |
| Enflurane  | Stable heart rate  
Skeletal muscle relaxation | EEG seizure activity  
Depression of myocardial contractility |
| Isoflurane | Decreases cerebral metabolic rate  
Cardiac output maintained  
Rapid uptake and elimination | Tachycardia at greater concentration |
| Desflurane | Rapid uptake and elimination  
Nonpungent  
Less depression of myocardial contractility  
Stable heart rate | Airway irritation  
Tachycardia with rapid increase in inspired concentration  
Requires specialized vaporizer for administration  
Expensive unless low flows are used  
Reacts with CO₂ absorbents  
Inorganic fluoride release  
Expensive unless low flows are used |
| Sevoflurane | Rapid uptake and elimination  
Nonpungent  
Less depression of myocardial contractility  
Stable heart rate | Reacts with CO₂ absorbents  
Inorganic fluoride release  
Expensive unless low flows are used  
Stable heart rate |
High-dose narcotics are an alternative form of anesthesia and offer an advantage of hemodynamic stability and lack of myocardial depression. The disadvantage is the requirement for postoperative ventilation. Recently, an ultra-short-acting narcotic (remifentanil) was introduced, negating the need for prolonged ventilation. There has been no difference in survival or major morbidity between a high-dose narcotic technique and inhalation-based technique. Therefore, most anesthesiologists use a “balanced” technique of lower doses of narcotics with an inhalational agent.

An alternative anesthetic agent is intravenous propofol, which is an alkyl phenol that can be used for both induction and maintenance of general anesthesia. It can result in profound hypotension secondary to reduced arterial blood pressure with no change in heart rate. It has a rapid clearance with few residual effects on awakening; however, it is expensive.

Regional Anesthesia
Regional anesthesia includes the techniques of spinal and epidural anesthesia, as well as peripheral nerve blocks. Peripheral techniques offer the advantage of being associated with minimal or no hemodynamic effects. In contrast, spinal or epidural techniques are associated with sympathetic blockade, which can lead to reduction in blood pressure, reflex sympathetic activation above the level of the blockade, and slowing of heart rate.

The associated autonomic effects of spinal anesthesia occur sooner than the same anesthetic agent administered epidurally. Since a catheter is usually left in place for epidural anesthesia, it can be more easily titrated. Improved outcomes have been demonstrated with a combined regional and general anesthetic approach for patients with CAD, particularly in those undergoing vascular surgery (128). One study noted a decreased incidence of all-cause cardiac morbidity with no difference in acute MI or cardiac death in patients receiving combined general plus regional anesthesia for infrainguinal surgery (129). Another study using epidural anesthesia for infrainguinal surgery followed by epidural analgesia versus general anesthesia plus postoperative intravenous patient-controlled analgesia showed no difference in cardiac morbidity between the two groups (130). A third study randomized patients to epidural, spinal, and general anesthesia and found no difference in cardiac outcome (131). Importantly, those patients who had a failed regional technique had the highest incidence of cardiac morbidity. The same findings are true for patients undergoing aortic surgery (132,133).

Monitored Anesthetic Care
In a large-scale epidemiological study, MAC was associated with increased 30-day mortality in a univariate analysis, although it did not remain significant in multivariate analysis (121). The major concern with MAC is the ability to adequately block the stress response, including tachycardia. Although MAC can supplement analgesia, the ability to provide good local anesthesia is important.

Pulmonary Artery Catheterization
Historically, pulmonary artery (PA) catheters were widely used in high-risk patients undergoing major noncardiac surgery, with the assumption that better understanding of cardiac filling pressures and cardiac output would lead to improved outcomes. However, there have been several randomized studies in which placement of a PA catheter perioperatively did not alter cardiac morbidity (134–136). Recent studies have shown a threefold, increased incidence of major postoperative cardiac events and a higher rate of pulmonary embolism in the PA catheter group than in those in the standard care group.
(134–138). The American Society of Anesthesiologists advocates reserving use of the PA catheter for those circumstances in which there is a high-risk patient undergoing a high-risk surgery, when the PA catheter will make a difference in medical management (139).

**Heart Rate Control**

Increases in heart rate cause increases in myocardial oxygen demand that can precipitate myocardial ischemia in patients with known CAD. Studies have supported a causal relationship between tachycardia and intraoperative myocardial ischemia (78). Attenuation of the heart rate response and control of exaggerated sympathetic responses in the perioperative period with β blockers may limit the development of myocardial ischemia and infarction.

**Anemia**

Anemia has also been associated with an increased incidence of perioperative myocardial ischemia. In a small retrospective study of patients undergoing infrainguinal bypass surgery, a hematocrit lower than 27% was associated with a significantly increased risk of postoperative MI (140). A higher rate of myocardial ischemia was noted in patients undergoing radical prostatectomy who had a hematocrit 28% or less compared with those with a higher hematocrit, although there was no difference in the rate of major morbidity (141).

**Maintenance of Body Temperature**

Hypothermia has also been associated with an increased incidence of myocardial ischemia in vascular surgery patients (142). In a randomized trial involving patients either undergoing vascular surgery or with known risk factors for CAD, use of forced air warming to maintain normothermia was associated with a significant reduction in cardiac morbidity and myocardial ischemia for the first 24 postoperative hours (143). Therefore, maintenance of normothermia should be a goal of perioperative management.

**Perioperative Arrhythmias**

The incidence of arrhythmias during noncardiac surgery varies widely and their prognostic importance is unclear (144). High-grade atrioventricular block, symptomatic ventricular arrhythmias in the presence of underlying heart disease, and supraventricular arrhythmias with an uncontrolled ventricular response are considered major clinical predictors of increased perioperative risk (11). The management of perioperative ventricular arrhythmias is not well studied and is generally considered to be the same as that for the nonsurgical patient. Reversible causes such as electrolyte disturbances, acid-base abnormalities, or decompensated CHF should be corrected. A search for underlying cardiac or pulmonary disease or for potential drug toxicity is essential. Significant perioperative ventricular arrhythmias do not often require therapy unless they are associated with myocardial ischemia, significant valvular disease, left ventricular dysfunction, or hemodynamic compromise. No studies support the suppression of preoperative arrhythmias with antiarrhythmics to reduce surgical morbidity and mortality. The use of perioperative β blockers may be beneficial.

One study in patients undergoing noncardiac surgery showed that major ventricular arrhythmias (>30 ventricular ectopic beats/hr or ventricular tachycardia) detected with
the use of continuous ECG monitoring occurred in 44% of patients and were not associated with clinical symptoms (144). Patients with CHF, ECG evidence of MI, or a history of tobacco use had a higher incidence of preoperative arrhythmias. Nonfatal myocardial ischemia or cardiac death was not more frequent in patients with these arrhythmias so that aggressive perioperative therapy may not be required.

**Surveillance for Perioperative MI**

The optimal and most cost-effective strategy for monitoring high-risk patients for major cardiac morbidity after noncardiac surgery is unknown. Postoperative myocardial ischemia or infarction is often clinically silent, most likely due to the confounding effects of analgesics. Creatine kinase (CK)-MB has been shown to be less specific than cardiac troponins for the detection of MI postoperatively (145). Non-ST-elevation MI occurs more often than ST-elevation MI perioperatively. In one study of diabetic and hypertensive patients, a postoperative daily ECG plus symptom-directed CK-MB isoenzymes yielded the best sensitivity and specificity for detecting MI (146).

Myocardium-specific enzymes such as cardiac troponins (I or T) are quite sensitive in the detection of perioperative MI. In one study of patients undergoing high-risk surgery, eight patients sustained a perioperative MI, as confirmed by the presence of new segmental WMAs, and all had elevations of cardiac troponin I (cTn-I), while six patients had elevated CK-MB (147). Troponin I had a specificity of 99%, while CK-MB had a specificity of 81%. Other studies have confirmed the clinical utility of cardiac troponins in the perioperative setting (148,149).

Traditionally, perioperative MI was associated with a 30% to 50% short-term mortality (7). With greater perioperative surveillance, more asymptomatic MIs are being detected. More recent series have reported that perioperative MI is associated with a short-term mortality of up to 20% (35,36). One study demonstrated significantly worse survival in patients who sustained a perioperative cardiac event compared with those who did not (150). A retrospective study of a cohort of patients who underwent major vascular surgery found that survival was significantly less for those who had a symptomatic perioperative MI (151). By contrast, asymptomatic MI, diagnosed by elevated cardiac enzymes, was not associated with worse survival. Elevated troponin-T levels have been shown to be associated with an increased incidence of cardiovascular complications within six months of surgery (152). In a study of patients undergoing vascular surgery, where cTn-I levels were measured immediately after surgery and on three consecutive postoperative days, 12% had elevated troponin I levels, which was associated with a sixfold increased risk of six-month mortality and a 27-fold increased risk of MI (153). Le Manach and colleagues studied 1152 consecutive patients who underwent abdominal infrarenal aortic surgery, and identified four patterns of cTn-I release after surgery. One group did not have any abnormal levels, while a second group had only mild elevations of cTn-I. It is interesting to note that two groups demonstrated elevations of cTn-I consistent with a perioperative MI. One demonstrated acute (<24 hours) and early elevations of cTn-I above threshold, and the other demonstrated prolonged low levels of cTn-I release, followed by a delayed (>24 hours) elevation of cTn-I. The authors suggest that these two different patterns represent two distinct pathophysiologies: acute coronary occlusion for early morbidity and prolonged myocardial ischemia for late events. Further research will be required to determine the implications of asymptomatic elevated postoperative cardiac enzymes on outcomes.

The ACC/AHA guidelines recommend the use of cardiac biomarkers for patients at high risk and those with clinical, ECG, or hemodynamic evidence of cardiovascular dysfunction (11).
Postoperative Analgesia

If postoperative tachycardia and catecholamine surges lead to cardiac events, the more intense analgesia regimens may be beneficial in improving perioperative outcomes. Additionally, there is growing interest in the role of postoperative analgesia in reducing the hypercoagulable state, as well as providing other benefits to the geriatric patient, such as reduced delirium. Studies comparing general with regional anesthesia have demonstrated reduced platelet aggregability in the epidural group (154). Future research will focus on how to best deliver postoperative analgesia.

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Disability and Frailty in Older Patients with Cardiovascular Disease

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INTRODUCTION

Functional status plays an important role in maintenance of quality of life as people age. When an older person is admitted to the hospital, the best predictor of hospital mortality is the ability to perform routine activities of daily living (ADLs) (1). Loss of independence in even one ADL dramatically increases the chances of an older person either dying or requiring nursing-home placement within six months following hospital admission (1,2). Moreover, loss of ADLs is a better predictor of outcome than the Charlson comorbidity index or the New York Heart Association functional class.

Nagi has created a simple model of the pathway to disability (3,4). In this model, active pathology (e.g., heart failure) leads to impairment in bodily functions (e.g., dyspnea), which leads to functional limitations (e.g., walking, stair climbing, poor memory), and finally to disability (Fig. 1). In this model, disability is defined as a limitation in the performance of work or in the tasks essential to allow a person to live independently.

The disablement process plays an important role in the determination of health-related quality of life, often assessed with the short form (SF)–36 questionnaire. The more cardiovascular-related diseases a person has (i.e., hypertension, diabetes, angina pectoris, heart failure, myocardial infarction), the lower the SF-36 score (5). This assessment is true for all eight domains of health-related quality of life (physical function, role-physical, bodily pain, general health, vitality, social function, role-emotional, and mental health). In addition, each cardiovascular disorder is individually related to the different domains, with the strongest associations being for angina and heart failure.

Similarly, as the number of comorbid diseases increases, so too does the likelihood of disability. The conditions most associated with the development of disability are hip
fracture, stroke, arthritis, and heart disease (6). The number of hospitalizations (i.e., acute events) is also a strong predictor of disability (7). In an analysis combining data from the 2001 Mexican Health and Aging Study (n = 4872) and the Hispanic Established Population for Epidemiologic Studies of the Elderly (n = 3050), the likelihood of disability due to comorbid diseases was most closely linked to diabetes, stroke, and heart attack (8). In the Framingham study, angina pectoris was the best cardiovascular predictor of disability, while heart failure only predicted disability in women (9).

These studies clearly implicate cardiovascular disease and related hospitalizations as important factors contributing to disability and impaired quality of life in older adults. This chapter focuses on the role of heart disease in the pathophysiology of frailty. Frailty represents a form of predisability associated with both impairments and limitations.

**FRAILTY—DEFINITION**

Frailty is a condition in which a person has impaired ability to carry out routine activities that exceeds normal age-related physiological deterioration. A frail person is at increased

**Figure 1** The pathway to disability in heart disease. *Abbreviations: ADLs, activities of daily living; IADLs, instrumental activities of daily living.*
risk of developing disability when exposed to stressful conditions such as hospitalization for an acute medical illness.

Fried et al. (10,11) have objectively defined frailty as the presence of three or more of the following:

- Weight loss (10 lbs in one year)
- Exhaustion (self-report)
- Weakness (grip strength; lowest 20%)
- Walking speed (15 ft; slowest 20%)
- Low physical activity (kcal/wk; lowest 20%)

Individuals with one or two of these factors are considered prefrail. Using this definition, the prevalence of frailty in a community-dwelling population of individuals aged 65 years or older was 6.9%, and the four-year incidence of frailty was 7.2% (11).

Another objective definition of frailty utilizes the FRAIL mnemonic:

- Fatigue (self report)
- Resistance/power (inability to climb one flight of stairs)
- Activity (inability to walk one block without stopping)
- Illness (more than three illnesses diagnosed)
- Loss of weight (5% in six months)

A positive score for frailty is three out of five. Alternatively, Rockwood (12) considers frailty merely to be a reflection of the number of underlying diseases in a person.

**FRAILTY AND HEART DISEASE**

Cacciatore et al. (13) studied 1259 older subjects with a nine-year follow-up. In this population, frailty was more predictive of mortality in persons with chronic heart failure than in the general population.

Chronic heart failure is a classical condition that predisposes to frailty. It is associated with a decline in VO₂max leading to reduced mobility and strength. It can also be associated with anorexia and declines in both lean and fat mass (cardiac cachexia). Activation of the renin-angiotensin system, and of angiotensin II in particular, leads to an increased rate of cleavage of actinomysin, with resulting clearance of muscle protein by the ubiquitin-proteasome system, resulting in accelerated loss of muscle mass (sarcopenia).

Coronary artery disease (CAD) results in decreased mobility because of angina pectoris and dyspnea. In addition, persons with CAD often have peripheral arterial disease that may lead to decreased walking time and a loss of lower limb muscle. This combination provides “fertile soil” for frailty to develop.

In the Cardiovascular Health Study, subclinical cardiovascular disease (i.e., asymptomatic carotid intima-media thickening, abnormal ankle-arm blood pressure index, or decreased left ventricular ejection fraction) was present in 37% of older adults and was a strong independent predictor of frailty (14). Thus, the presence of clinical or subclinical cardiovascular disease is a potent risk factor for the development of frailty in older adults.

**PATHOPHYSIOLOGY OF FRAILTY**

Frailty occurs as an interaction between aging physiology, environment, and disease. The major lifestyle factor is physical activity, including formal exercise, e.g., endurance, resistance, and balance exercises, as well as spontaneous physical activity, e.g., the
distance walked each day or the time spent gardening. Food intake leading to either obesity or undernutrition represents a second lifestyle factor involved in the pathogenesis of frailty.

Factors contributing to frailty include sarcopenia and decline in executive function. Syndromes that can interact with heart failure to foster frailty include chronic pain, anemia, and cachexia. Anemia is an independent predictor of physical disability in older heart failure patients (15).

As noted above, sarcopenia refers to the loss of muscle mass that occurs with aging (16). Sarcopenia is considered pathological when the muscle mass is 2 SD below that of a young person. It is best measured using DEXA and dividing the appendicular muscle (lean) mass by height squared. Using this approach, approximately 18% of 70-year-old persons and 50% of 80-year-old persons are sarcopenic (17). Importantly, with aging, loss of strength and power is greater than loss of muscle mass. Many older persons also develop fat infiltration into their muscles, i.e., myosteatosis, which further decreases muscle function (18). Men with moderate sarcopenia have an adjusted odds ratio for physical disability of 3.65 relative to men without sarcopenia, while the adjusted odds ratio is 4.71 in men with more marked sarcopenia; corresponding odds ratios in women are 1.41 and 2.96 (19). While persons with moderate obesity and no sarcopenia have good outcomes, obesity associated with sarcopenia, i.e., sarcopenic obesity or “fat frail,” is a strong independent predictor of future disability and mortality (20).

The causes of sarcopenia are summarized in Table 1. Genetic factors and low birth weight have been associated with poor grip strength at age 70 years (21). In accordance with the adage “use it or lose it,” lack of physical exercise, in particular resistance exercise, is a major cause of loss of muscle mass. A daily energy intake of less than 21 kcal/kg leads to sarcopenia and frailty (22). To maintain muscle mass, most older persons require between 1.2 and 1.5 g/kg/day of protein, as opposed to the recommended 0.8 g/kg/day (23). Besides acting as building blocks for muscle, branched chain amino acids (leucine, isoleucine, valine) promote protein synthesis and inhibit proteolysis (24). Creatine intake has been shown to enhance lean mass and power in older persons performing resistance exercise (25). Insulin resistance leads to triglyceride accumulation in muscle and decreased strength (18).

Anabolic steroids play a key role in maintaining muscle mass and strength (26). Anabolic steroids increase protein synthesis and promote the conversion of stem cells to

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muscle satellite cells (cells responsible for skeletal muscle repair). Testosterone increases muscle mass, strength, and function in older persons (27,28), and it has been shown to increase functional capacity and reduce symptoms in older men with moderate heart failure (29). Nandrolone, another anabolic steroid, increases muscle mass and strength in older women (30). Selective androgen receptor molecules (SARMs) increase muscle strength and prevent bone loss while having no adverse effects on the prostate gland.

Ostarine is a SARM that has been shown to increase lean mass and power in men and women older than 60 years. In contrast, dehydroepiandrosterone at a dose of 50 mg daily for one year failed to increase muscle mass or strength (31).

Growth hormone increases nitrogen retention and muscle mass but fails to increase strength. Ghrelin, a peptide hormone secreted primarily from the fundus of the stomach, stimulates release of growth hormone and increases food intake and muscle mass. In addition, preliminary data indicate that ghrelin improves left ventricular function and exercise capacity in older persons with heart failure (32). Growth hormone acts by increasing insulin growth factor-1 (IGF-1), which increases muscle protein synthesis. Mechanogrowth factor is a splicing variant of IGF-1. It is increased by resistance exercise and enhances muscle strength by increasing satellite cell recruitment. Stem cells with mechanogrowth factor have been shown to reverse sarcopenia in older rats (33).

Vitamin D levels decline throughout life (34), and levels less than 30 ng/mL are associated with sarcopenia, falls, hip fracture, and disability (35). Vitamin D replacement reduces the risk of these conditions.

Myostatin is a protein that inhibits satellite cell proliferation. Inhibition of myostatin results in muscle regeneration. Early studies with myostatin antibodies in humans show promise for restoring skeletal muscle mass. At present, there are no data on the effects of myostatin antibodies on myocardial muscle.

Cytokines, such as tumor necrosis factor \( \alpha \) and interleukin-6, are associated with loss of muscle mass, decreased strength, and poor physical function (36). Cytokine elevation is also associated with anemia, hypoalbuminemia, low cholesterol, and loss of bone mineral. Moreover, it has been suggested that cytokines may play a fundamental role in the aging process (36).

Motor units play a key role in the maintenance of muscle mass, but motor unit firing rates decrease with aging (37). In addition, there is a decline in the ciliary neurotrophic factor (CNTF) that correlates with a decline in muscle mass and strength. Conversely, CNTF administration has been shown to increase soleus muscle mass twofold (38).

Peripheral arterial disease leads to decreased physical activity and muscle apoptosis, resulting in sarcopenia and diminished muscle strength.

In summary, the pathophysiology of frailty and sarcopenia are complex and multifactorial. In addition, interactions between these conditions and cardiovascular disease are bidirectional, such that cardiovascular disease contributes to the development and progression of frailty and sarcopenia, while the latter conditions accelerate the functional decline and disability associated with cardiovascular disorders in older people.

**CARDIAC CACHEXIA**

Cachexia or wasting disease, a condition in which anorexia and systemic inflammation lead to marked weight loss (both muscle and fat), occurs in 10% to 35% of patients with heart failure (39) and is a major cause of disability in such patients. Nonintentional weight loss of greater than or equal to 7.5% of body weight is associated with a marked increase in mortality (40), independent of \( \text{VO}_{2}\text{max} \), left ventricular ejection fraction, New York
Heart Association class, serum sodium, or age. Similarly, low cholesterol is highly predictive of mortality in heart failure (41). Moreover, heart failure patients with body adipose tissue content in the highest quartile have improved survival compared with those in the lowest quartile (42). Thus, obesity and overweight are “reverse” risk factors for mortality in patients with chronic heart failure, while weight loss and cachexia are strongly associated with functional decline and death (43). In addition, these associations are in part related to the presence of elevated cytokines (44).

The causes of cachexia in older persons with heart failure are multifactorial and include:

- Anorexia
- Early satiation
- Dyspepsia
- Protein enteropathy
- Abnormal catecholamine kinetics
- Malabsorption
- Increased metabolic rate
- Cytokine excess
- Medications
- Depression

Discussion of each of these factors is beyond the scope of this chapter, but it is becoming increasingly recognized that prevention of disability in older persons with heart failure requires prevention of weight loss.

CONCLUSION

Disability is a common outcome of heart disease in older persons, and there is a growing body of evidence linking cardiovascular disease with sarcopenia, frailty, and progressive functional decline. Minimizing disability in older cardiac patients requires aggressive treatment of symptoms, especially angina and dyspnea, to enable such patients to engage in optimal levels of physical activity. In addition, regular aerobic and resistance exercise is, at present, the most effective means for preventing disability and maintaining functional capacity, independence, and quality of life in older cardiac patients (45,46). Proper nutrition, emphasizing prevention of weight loss, is also crucial for limiting the adverse impact of cardiovascular disease on functional outcomes. The role of other interventions, such as treatment of anemia and the use of anabolic hormones, for the prevention and management of disability in older cardiac patients requires further investigation.

REFERENCES


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Ethical Decisions and End-of-Life Care in Older Patients with Cardiovascular Disease

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Death is the only certainty in life. Doctors should allow their patients to make the most out of living but not to fight dying. It is the job of the physician to guide his or her patients' health as long as a measure of happiness is achievable, and to make their passing comfortable and dignified when death is near and unavoidable (1). After all, life is measured by the richness of its experiences rather than by the length of its days. It is not a great achievement to prolong the years of mindless existence in a state deemed by the patient to be a fate worse than death (2). Research should focus on reducing suffering and prolonging life worth living.

The health care of Americans costs more than twice that of the British ($5993 vs. $2861 per individual per year). Americans live an average of 77.9 years, of which less than 70 years are independent. By contrast, the British live an average of 79 years, of which more than 70 years are spent in independent living. The Japanese live an average of 82.8 years with fewer than five years spent in institutionalized, dependent care. In Japan, the cost of health care per individual is $2856 per year (3). More dollars do not equate to more health. The United States may have the best-educated doctors, the best hospitals, and the most advanced technology, but it does not have the best health care system (4). The 2000 report of the World Health Organization ranked the U.S. health care system 37th among nations—between Costa Rica and Slovenia—on the basis of dollars spent in relation to the health care provided. Ten percent of American children lack basic health coverage and more than 15% of American citizens lack health insurance. Furthermore, a minority of medical textbooks have chapters on end-of-life care, although mortality rates for many diseases are often provided (5). This deficiency needs to be addressed and corrected by the medical establishment.

In this chapter, we shall focus attention on how ethical factors can and should influence the management of cardiovascular disease in elderly individuals. But we shall
also urge thoughtful and caring physicians, regardless of their practice orientation or the age of their patients, to direct attention to identifying or treating cardiovascular risk factors and diseases. Once identified, efforts to minimize the potentially adverse effects of cardiovascular disease and associated therapies should be initiated in ALL patients and in society at large.

PREVENTIVE EFFORTS

Cardiovascular disease is epidemic in most countries (6). Moreover, many cardiovascular diseases are preventable or modifiable, provided the individual recognizes early enough the existence of deleterious behaviors and risk factors, and resolves to correct them. Such a goal is more likely to be attained if all physicians involved in an individual’s care focus attention on these factors, especially obesity, lack of physical activity, and smoking. According to Massie (7), nearly 60% of adults in the United States are overweight or obese. Similarly, fewer than half of American adults engage in regular exercise and over 20% are regular users of tobacco. Clearly, reduction or eradication of these adverse behaviors would substantially reduce the burden of cardiovascular disease.

More than one-half of men and women older than 65 years have significant hypertension. No longer can even a mildly elevated systolic blood pressure (BP), even in older persons, be considered a “normal” or a “physiological” component of the aging process. Indeed, data from the Framingham Heart Study indicate that in both older and younger individuals (8), the risk of coronary heart disease increases progressively at levels of systolic BP greater than or equal to 120 mmHg (9). Therefore, diagnosis and appropriate treatment of hypertension is warranted in people of all ages.

The prevalence of impaired glucose tolerance, diabetes mellitus, and dyslipidemia increases with age. Older adults should be screened for these conditions and, if present, therapy should be initiated in accordance with current practice guidelines.

Prevention of cardiovascular disease, through modification of adverse behaviors and risk factors, is more beneficial and more cost-effective than treatment of the complications of cardiovascular disease occurring years later. Physicians, health care systems, and payers need to realign priorities to emphasize disease prevention whenever feasible.

EVOLUTION OF THE PRACTICE OF INFORMED CONSENT

Ethical considerations of informed consent in the practice of medicine evolved from the use of human subjects in clinical investigation. In 1973, Senator Edward Kennedy introduced legislation to establish the National Commission for the Protection of Human Subjects (10). Soon thereafter, the Doctrine of Informed Consent was established (11). As a result, patients must now be informed about the risks and expected outcomes of all medical procedures, and consent must be provided prior to performing the procedure.

During the early 1970s, both the medical profession and society at large accepted the view that all knowledge and skills did not have to be utilized in all individuals at all times; i.e., interventions could be applied selectively in accordance with individual circumstances. In addition, it became clear that society at large was not willing to grant physicians unlimited supremacy in caring for all medical problems. Assistance from the courts was sought to resolve many areas of conflict and even to define the authority of physicians under certain conditions.
COURTS RESOLVE MEDICAL CONFLICTS

In the early 1970s, many physicians as well as lay people questioned whether all pregnancies should be guided toward a full-term delivery. For example, should a fetus with serious structural and/or functional abnormalities be delivered prematurely with the goal of spontaneous death, or should society and/or physicians demand that every effort be made to sustain the fetus, seeking a full-term birth and survival, even with an anticipated markedly compromised quality of life? Until that time, it was widely accepted that “everything possible” should be done to preserve all life, including that of an unborn, deformed fetus (12).

This question was finally considered by the U.S. Supreme Court under the legal action of Roe v. Wade. The court ruled that “a woman has the right to an abortion without interference from the government in the first trimester of pregnancy.” The court concluded that “it is a part of her right to privacy,” although the court maintained that the “right to privacy is not absolute.” Conversely, the court granted the states the right to intervene in the second and third trimesters of pregnancy. Since then, many states have established laws regarding interruption/protection of pregnancy in the second and third trimesters (11).

The complexity of care for an individual with persistent loss of consciousness was recorded in the terminal case history of Karen Ann Quinlan. On the night of April 15, 1975, the 22-year-old woman became comatose and was admitted to a New Jersey hospital (12). Some evidence suggested that the coma evolved as a result of ingesting a combination of prescription medication and alcohol. Shortly after admission to the hospital, the patient was placed on a respirator. After several months, during which time there was no evidence for significant neurological recovery, the patient’s parents asked the physician to take their daughter off the respirator.

The Quinlans were practicing Catholics and had sought guidance from the Church regarding continuous use of the respirator. Their priest told them that the respirator could be defined as “extraordinary care,” and that returning Karen to her “natural state” (i.e., taking her off the respirator) was a morally correct action, even if she should die (13).

The primary physician at first agreed to remove the respirator, but then feared that if Karen died there could be legal ramifications. He, therefore, refused to remove the device.

The Quinlans asked a lower court in New Jersey to order the physician and the hospital to remove the respirator, but the court refused to accept the case. The Quinlans then sought help from the Supreme Court of the State of New Jersey. The court heard the case in June 1976 and agreed that the family did have the right to order removal of the respirator. This decision marked the first time that a court gave orders regarding therapy for a specific patient that did not support the judgment of the physician. Ms. Quinlan survived in a comatose state for nine years after removal of the respirator, thus demonstrating how difficult it can be, even for highly qualified physicians, to predict when death will actually occur.

This was indeed a landmark case. It involved not just the patient’s right to die or the concept of living wills. It involved a far more basic issue—who rules at the bedside (14)? The Quinlan case was a conflict between physicians, on the one hand, and patients and families and legal advisors on the other. Prior to the court’s ruling, the physician was presumed to have the primary role in representing the patient’s interests. As a result of the Quinlan case, the courts and legal counsel assumed an increased role as patient advocates.

In rendering its opinion in the Quinlan case, the New Jersey Supreme Court referred to the Roe v. Wade decision, noting that the U.S. Supreme Court had reduced the supremacy of the physician. The Court stated that:
Presumably the Right to Privacy is broad enough to encompass a patient’s decision to decline medical treatment under such circumstances, in much the same way that it is broad enough to encompass a woman’s decision to terminate pregnancy under certain conditions.

Another landmark case was that of Nancy Cruzan (11–14). Ms. Cruzan, a woman in her 20s, lost control of her car in 1983. The vehicle overturned and she was found lying face down in a ditch, without detectible respiratory or cardiac function. It was later estimated that she had been deprived of oxygen for about 12 to 14 minutes.

Paramedics were able to restore her cardiac and respiratory function and she was taken to a hospital where she received maximum acute care. She remained in a coma for three weeks and then progressed to a condition in which she did not relate to her environment, and she was diagnosed as being in a persistent vegetative state. A gastrostomy tube was implanted to improve her nutrition. After several weeks, the parents asked the hospital authorities to remove the tube and let their daughter die peacefully.

The remaining life of Nancy Cruzan will be described in some detail because it emphasizes the importance of a person, even in her 20s, having an advance care plan. Nancy had completed no such document, but she allegedly had made statements to a friend and roommate that she “would not want to live as a vegetable.” Her parents were confident that indeed Nancy would rather die than live as she was.

However, the doctors and hospital authorities refused to honor the parents’ request without court approval, which was sought by the parents. The trial court initially approved termination of the gastrostomy tube. That decision was contested by the state of Missouri and reversed by the State Supreme Court, and the case was taken to the U.S. Supreme Court, which accepted the Missouri Supreme Court’s ruling, stating that individual states do have the right to demand that a person must receive life-sustaining treatments (regardless of the family’s wishes) unless that person established clearly and convincingly, while competent, that he or she would not want to be kept alive by artificial means. Despite lack of support from the U.S. Supreme Court, the parents persisted with their desire to terminate the life of their comatose daughter. They identified new, more persuasive witnesses. In addition, the Missouri legislature revised the state laws to allow the family or appointed guardian of a permanently unconscious patient to discontinue life-sustaining measures, provided there is clear and convincing evidence that the condition is permanent and irreversible, and the state of Missouri withdrew from the Cruzan case stating that “it has no interest in the outcome of this litigation.”

The parents took the case back to the original trial court in Missouri. After hearing the testimony from the new witnesses, the judge ruled that there was now clear and convincing evidence that Ms. Cruzan would not want to continue to live in a vegetative state. The gastrostomy tube, which had kept the patient alive for seven years, was removed and 12 days later Ms. Cruzan died.

The activities related to Ms. Cruzan’s case were widely publicized. Many people supported removal of the feeding tube and possibly hastening death, while many others favored maintaining nutrition and preserving life even in a vegetative state. As a result, when Nancy Cruzan died in the Missouri Rehabilitative Center, 35 armed guards patrolled the premises to prevent the euthanasia opponents, who were camped outside, from breaking into her room to forcibly reinsert the tube. The police arrested 19 individuals who stormed the center in an attempt to locate Ms. Cruzan’s room.

More recently, issues related to patient autonomy and end-of-life care came under public scrutiny in the case of Terri Schiavo (15). On March 31, 2005, Teresa Marie Schiavo
died at the age of 41 years, almost two weeks after a Florida Court ordered the removal of the percutaneous endoscopic gastrointestinal tube that had been providing Mrs. Schiavo with hydration and nutrition.

On February 25, 1990, Terri Schiavo suffered cardiac arrest, apparently due to a potassium imbalance brought on by bulimia that her husband, Michael Schiavo, and her parents, the Schindlers, were not aware of. Cardiopulmonary resuscitation (CPR) was administered and effective spontaneous cardiac and respiratory function was restored. However, severe brain damage had already occurred because of prolonged anoxia. Mr. Schiavo was appointed guardian of his wife without objection from the Schindlers. In 1992, two malpractice suits in Mrs. Schiavo’s case were successful, and the remunerations were placed in a trust for her care. Subsequently, Terri’s case was adjudicated in several state and federal courts, but was rejected multiple times by the U.S. Supreme Court. The case gained publicity because of the actions of special interest groups and efforts by the Florida governor and legislature to block the court order to remove Terri’s feeding tube by passing what became known as Terri’s Law. The case was further publicized when the U.S. Congress convened for a special weekend session to pass legislation stating that “Terri deserves a second chance,” followed by the travel of the U.S. president from his Texas ranch to Washington after midnight to sign the newly passed emergency legislation, proclaiming that “we should err on the side of life.” In addition, there were pronouncements from influential members of Congress claiming that society should have a say in this matter (16).

To resolve these issues, the courts had to address two questions:

1. Was Mrs. Schiavo in a permanent vegetative state? To answer this question, the court-appointed national expert ascertained that there was no evidence of higher brain function, and that the facial grimacing, yawning, roving of the eyeballs, and other motor activities reflected reflex brain stem activity and did not represent awareness (17). This view was subsequently confirmed by the autopsy findings of severe diffuse brain atrophy (18).

2. Was there clear and convincing evidence that Terri did not want to linger in a persistent vegetative state? To resolve this issue, the courts painstakingly interviewed those who knew or talked to Terri beforehand and determined that she would not have wanted to exist in such a state of unawareness maintained by artificial means.

On the basis of these findings, the Florida Court ordered removal of Terri’s feeding tube. This case reinforces the need for all of us to express in writing our medical choices before we become incapable of doing so in order to avoid leaving these personal decisions to the machinations of the legal system.

In spite of the seemingly conflicting court rulings on the issue of futile care, no physician has ever been indicted, let alone convicted, for withholding care deemed unnecessary by reasonable medical standards. This fact may seem surprising when one considers the prevailing view among practicing physicians that they should not withhold care because of the potential for legal repercussions. In the case People v. Barber, heard by a Los Angeles court in 1983, nurses complained to the state prosecutor that physicians withdrew treatment, including feeding and hydration, from a terminally ill patient and “watched him die” (19). The court dismissed the case on the basis that there was...
that the attending physician sat back and watched a person starve to death is to ignore the state of bad health of the patient, Mr. Herbert.

Support for the physician withholding treatment was particularly strong in the Spring v. Massachusetts case, heard in the Supreme Judicial Court in 1980 (20). In this case, the court not only upheld that an incompetent person has the same right to respect, dignity, and freedom of choice as competent people, but also sent a message to treating physicians: “...little need be said about criminal liability; there is precious little precedent, and what there is suggests that the doctor will be protected if he acts in a good faith judgment that is not grievously unreasonable by medical standards.”

The legal scholar, Dr. Allan Meisel, professor of law and medicine at the University of Pittsburgh and the author of Right to Die, a legal compendium originally published in 1989 and now in its third edition, summarized the developing legal consensus in 1992 (21). He indicated that the bulk of court opinions have been generally supportive of the principle that determination of the futility of care is a decision to be made by the medical profession. Artificial feeding and nutrition are regarded no differently than other intrusive medical treatments when it comes to end-of-life care. This is explicit in the Supreme Court ruling regarding Nancy Cruzan. These opinions suggest that physicians are under no obligation to seek consent from patients or families before withholding or withdrawing care that is deemed ineffective. Also, physicians are not exposing themselves to legal liability if their decision is reasonable by conventional medical standards. Of course, a caring, thoughtful physician would be expected to keep responsible members of the patient’s family informed about such important decisions.

One of the lessons learned from the Supreme Court discussions is that even if Ms. Cruzan had a standard living will, it would not have altered the course of action for her in Missouri or in other states that prohibit the natural process of dying (i.e., without interference) in permanently unconscious patients. This is because living wills are often written in vague and nonspecific language using terms such as “terminal illness,” “artificial means,” and “heroic measures,” all of which are subject to variable interpretations. For example, some argue that feeding and hydration are essential regardless of the mode of administration and therefore do not consider feeding tubes or intravenous lines as representing “artificial means” of support.

It is of interest that the U.S. Supreme Court rejected the wishes of the family to terminate Ms. Cruzan’s life support by a vote of 5 to 4. In dissenting, Justice William J. Brennan stated eloquently:

Too few people execute living wills or equivalent formal directives for such an evidentiary rule to ensure adequately that the wishes of an incompetent person will be honored. When a person tells family or close friends, however, that she does not want her life sustained artificially, she is expressing her wishes in the only terms familiar to her. To require more is unrealistic for all practical purposes. It precludes the rights of the patient to forgo life-sustaining treatment.

Teno et al. (22) noted that a minority of Americans execute living wills. Moreover, almost 90% of living wills are not medical scenario specific. In contrast, the Project GRACE (Guidelines for Resuscitation And Care at the End of Life) Advance Care Plan is medical scenario specific and enables primary-care physicians to comply with their patients’ choices for care at the end of life (23).

It should be noted that although living wills are often considered as being primarily intended for older adults, Karen Quinlan, Nancy Cruzan, and Terri Schiavo were all in
their 20s when they sustained severe brain damage. For this reason, many experts urge all individuals, 18 years and older, to have a well-documented Advance Care Plan (24,25).

To facilitate end-of-life planning and improve end-of-life care, the authors organized a State of Florida Consensus Development Conference in April 2000. A document clearly stating the individual’s wishes for care at the end of life was developed and is now available for general use in English and Spanish (23). This document, which has subsequently been updated, contains an Advance Care Plan that can be adapted by an individual to instruct their doctor(s) and other health care providers on how they wish to be treated during the last days of their life should they develop (1) an unconscious state, (2) permanent confusion, (3) total dependence, or (4) an end-stage disease or other debilitating end-stage condition. Specific instructions are provided about the use of CPR, surgery, blood products, antibiotics, or tube feedings under various end-of-life scenarios. The document also includes the name, address, and telephone numbers of a surrogate decision-maker for health care affairs in the event that the patient is no longer able to make such decisions. Once completed, the document can also be stored for immediate access at an Emergency Information Storage Center.

CARDIOPULMONARY RESUSCITATION

In 1979, Bernard Lown reported that 350,000 to 500,000 Americans died each year as a result of sudden cardiac arrest. By 1990, the incidence of sudden cardiac death had declined to about 300,000 per year despite the aging of the population (26). This reduction was attributed primarily to improved care of patients with cardiovascular disease (e.g., β blockers following myocardial infarction). In addition, the proportion of patients surviving sudden cardiac arrest increased as a result of prompt initiation of CPR and, in particular, timely administration of external thoracic electrical shocks to treat ventricular tachycardia and ventricular fibrillation, the most common mechanisms for sudden cardiac arrest (27).

Despite these advances, the overall success rate of CPR remains limited. Schneider and coworkers (28) reported a meta-analysis of 98 studies involving in-hospital CPR performed on 19,955 patients. Only 15% of the patients survived to be discharged from the hospital.

Thompson and coworkers (29) reviewed data on 316 patients with an average age of 63 years who were treated in the Seattle Heart Watch Program. They reported that 117 patients (37%) died prior to hospitalization (at the scene, in the ambulance, or in the emergency room); an additional 106 patients (34%) died in the hospital, despite successful resuscitation. Thus, only 93 patients (29%) were successfully resuscitated and survived to be discharged from the hospital.

Among patients initially resuscitated from sudden cardiac arrest, a sizable proportion sustain significant anoxic brain damage, resulting in moderate or severe cognitive impairment, or even brain death. Such cases often pose challenges to health care providers and patients’ families in determining the appropriate level of care (“do everything” vs. comfort measures only vs. withdrawal of support leading to a painless death). Resolving these issues may be particularly difficult when there are disagreements among family members or between physicians and family members. As a general principle, the previously expressed wishes of the patient take precedence over all other viewpoints. In this regard, a carefully executed Advance Care Plan can provide specific directions on how to proceed, while at the same time greatly relieving the family and caregivers of this considerable burden.
DO NOT RESUSCITATE

For many individuals, a sudden, essentially painless death might be viewed as a highly desirable event, perhaps even a blessing. Such might be the case for a patient with widespread cancer or extensive neurological impairment. These considerations, along with the limited efficacy of CPR and the potential for significant anoxic encephalopathy following restoration of a viable cardiac rhythm, have fueled discussions about withholding CPR in certain circumstances.

In 1974, the American Heart Association proposed that in some individuals with advanced debilitating diseases, a Do Not Resuscitate (DNR) order should be documented in the medical record (30).

In 1976, the Clinical Care Committee of the Massachusetts General Hospital developed recommendations for the treatment of hopelessly ill patients and for orders not to resuscitate (31). The DNR order intended that, in the event that the heart stopped contracting or the lungs ceased to function, no effort should be undertaken to revive the heart or place the patient on an assisted ventilation device. The patient’s chart should be clearly marked to indicate this plan.

The Committee determined that a DNR order was appropriate only when the patient’s disease fulfilled all three of the following criteria:

1. The disease is “irreversible” in the sense that no known therapeutic measures can be effective in reversing the course of the illness.
2. The physical status of the patient is “irreparable” in the sense that the course of illness has progressed beyond the capacity of existing knowledge and techniques to stem the process.
3. The patient’s death is “imminent” in the sense that in the ordinary course of events, death will occur within a period not exceeding two weeks.

The Committee also stipulated that the initial medical judgment regarding a DNR order be made by the physician primarily responsible for the patient’s care, after discussion with an ad hoc committee consisting not only of the other physicians, nurses, and other health care professionals active in the patient’s care, but also of at least one other staff physician not previously involved in caring for the patient.

Even with the medical staff’s recommendation, the Committee deemed that a DNR order would become effective only with the informed choice of a competent patient. If the patient was incompetent, all appropriate family members must be in agreement with the views of the medical staff.

In their original form, these guidelines imposed a tremendous burden on the treating physician, as a result of which they were rarely followed to the letter. Nonetheless, it became clear that unanimous approval of all involved family members was highly desirable. Unfortunately, this was not always possible, and the courts were not infrequently called upon to resolve conflicting opinions regarding the practice of DNR.

In considering CPR versus DNR for a given patient, CPR should be used only if the patient has a good chance of being restored to a conscious living state in which some degree of autonomy, even if limited, can be anticipated (32). Because the likelihood of successful outcome from CPR is often difficult to assess, the decision to undertake CPR can be challenging for the physician or other health care provider.

Physicians are trained from their earliest medical experience to act in favor of sustaining life. But this objective can conflict with another fundamental construct of medicine, the relief of suffering. Therefore, it is essential for the physician to have a frank and open discussion with all patients and family members designated to assume the role
of decision maker about the desirability of attempting CPR if a cardiac arrest occurs (33). Current policies in most hospitals require statements regarding such treatment to be included in the orders of the patient’s hospital chart. But such orders no longer need to be as detailed as those recommended by the Massachusetts General Hospital in 1976 (34).

Wagg et al. (34) have shown that physicians and nurses in the United States and the United Kingdom estimate a success rate of CPR that is at least double the actual success rate for in-hospital resuscitation. Success rates approaching 70% on television contribute further to public misinformation (35). These factors foster exaggerated promises from health care providers and unrealistic expectations by the lay public, leading to unreasonable demands followed by disappointments and blame-seeking when loved ones are lost. In contrast, when frail elderly individuals are informed that only a small percentage survive after out-of-hospital resuscitation, many opt to forego CPR when they suffer cardiopulmonary arrest in a nursing home or wherever they spend their final days.

Ideally, in the future most individuals will have given careful thought to the adoption of an Advance Care Plan. This plan should become a part of every adult’s important personal papers and medical/hospital records. Each caring physician should have a candid discussion with the patient and responsible relatives about their wishes for treatment should death become imminent and encourage proper documentation of these wishes.

A related issue is that in the past decade, the implantation of various cardiac devices in patients with cardiac impairment has soared. As patients near the end of life, these interventions become marginally beneficial and relatively more costly (36). Cardiologists bear the responsibility for advising their patients about the benefits and risks of such interventions, and also whether palliative care might be more desirable under certain circumstances. Training programs and cardiovascular societies have the responsibility to address these issues. “It takes a technician to recommend a certain procedure and a real doctor to advise against it” (37).

**EUTHANASIA AND PHYSICIAN-ASSISTED SUICIDE**

In 1997, the U.S. Supreme Court ruled that American citizens do not have a constitutional right to physician-assisted suicide. However, the court further stipulated that states are free to ban or permit this practice. Oregon has chosen to permit physician-assisted suicide in certain circumstances. The Oregon “Death with Dignity Act,” passed in October 1997 (38), allows the physician who has primary responsibility for managing a patient’s terminal illness to prescribe a dose of lethal medication that the patient may administer provided certain conditions are met. Death, confirmed by a consultant, should be expected within six months. The patient must make two oral requests and one written request for assisted suicide over a period of 15 days. Referral to a mental health professional is required if either the attending physician or the consultant is concerned that the patient’s judgment may be impaired by a mental disorder.

On January 17, 2006, the U.S. Supreme Court ruled 6 to 3 in favor of upholding the state of Oregon’s right to provide a qualifying terminally ill patient with a prescription for a lethal dose of barbiturates. This majority opinion of the U.S. Supreme Court was based on the view that it is up to the individual states, not the federal government, to regulate the practice and behavior of doctors. Legislation similar to Oregon’s is being debated in Wyoming, Washington, and California. (39)

In 1998, 24 Oregonians were given prescriptions for lethal doses of medication. Of these, 16 died after ingesting the medicine (40). The rest either died naturally without taking the medicine or elected not to take it.
In 1999, of 33 Oregonians who were given such prescriptions, 27 took their own lives. Participation was not found to be associated with low educational level, lack of health insurance, or poor access to hospice care.

Only 12% of the 1998 patients were married, raising concern that physician-assisted suicide would be requested mostly by patients lacking social support. However, in 1999, 44% of patients were married.

Autonomy and the desire to control the moment of dying were the most important factors driving terminally ill patients to request assisted suicide. In addition, in 1999, over half the patients raised the issue of pain and suffering as a contributing factor. In many instances, however, the fear of suffering was more pressing than actual pain. Importantly, of the 165 patients who requested suicide, more than one-third did so because they perceived themselves to be a burden to others. Only three of these received a prescription, suggesting that physicians were reluctant to accede to requests for assistance under these circumstances.

Oregon doctors granted one in six requests for lethal medications, and only 1 in 10 requests eventually resulted in suicide. “Physicians frequently made palliative care interventions which were helpful to patients and caused them to change their minds about assisted suicide,” reported Dr. Linda Ganzini, a geriatric psychiatrist at the Portland Veterans Medical Center (41,42). One-third of patients went to more than one doctor seeking assistance.

In the same issue of the New England Journal of Medicine, Drs. Amy Sullivan, Katrina Hedberg, and David Fleming (42) from the Oregon Health Division of the Centers for Disease Control and Prevention reported on the second year’s experience with legalized physician-assisted suicide in Oregon. The authors concluded, “In the second as compared with the first year of legalized physician-assisted suicide in Oregon, the number of patients who died after ingesting lethal medications increased, but it remained small in relation to the total number of persons in Oregon who died. Patients who request assistance with suicide appear to be motivated by several factors, including loss of autonomy and a determination to control the way in which they die.”

The Oregon experience has lent credence to both sides of the debate, for and against physician-assisted suicide. On the one hand, the law to legalize physician-assisted suicide in Oregon did not open the floodgates to mass executions. Less than 4 out of every 10,000 deaths occurred by lethal drug prescription. Most of these deaths were quick and uneventful.

On the other hand, the experience shows that with adequate attention to pain and anguish, in most cases it would not be necessary to consider the option of ending the life of another person; indeed, most of those who pursued this course expressed a strong need for autonomy and a desire to be in command of all aspects of their life and death.

Dick L. Willems and colleagues of Vrije Universiteit, Amsterdam, the Netherlands, (43) compared physicians’ attitudes in the United States with those from the Netherlands regarding physician-assisted suicide. They noted that physicians from the Netherlands have less restrictive views about physician-assisted suicide, particularly for patients who perceive themselves as being a burden to others. The authors of the present chapter do not advocate euthanasia or physician-assisted suicide, but rather a more natural course by which the patient is neither punished by unnecessary technological interventions nor encouraged to die before he or she is ready.

When asked, patients approaching the end of life indicate that they want to be free of pain and suffering, not have the dying process artificially prolonged by technology, not be a burden to others, retain the capacity to interact with loved ones, and maintain a sense of control (44). Cardiologists should understand that emphasis on quality of life and
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seeing through the patient’s eyes are imperative to caring for individuals as they near the end of life. The narrative skills, ability to communicate with patients and families about end-of-life issues, as well as understanding of what constitutes quality of care for the dying cardiac patient are paramount.

After all, to die well is the height of wisdom of life (45).

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Individuals 65 years of age or older currently account for over eighty percent of all cardiovascular disease-related deaths. With advances and breakthroughs in modern medicine that are allowing people to live longer, the number of older adults in this country will continue to grow exponentially over the next several decades. Cardiologists, geriatricians, and other clinicians caring for the elderly will require—at the very least—a basic understanding of cardiovascular disorders that commonly affect the older patient. In the Fourth Edition of this classic text, each chapter has been thoroughly updated to provide a comprehensive, yet readable overview of the epidemiology, pathophysiology, evaluation, and treatment of cardiovascular disorders in older adults.

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