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Update: Systemic Diseases and the Cardiovascular System (VII)

Cardiovascular Disease in the Elderly

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ABSTRACT

The aging of the population worldwide will result in increasing numbers of elderly patients, among whom heart disease is the leading cause of death. Changes in cardiovascular physiology with normal aging and prevalent comorbidities result in differences in the effects of common cardiac problems as well as the response to their treatments. Patient-centered goals of care such as maintenance of independence and reduction of symptoms may be preferred over increased longevity. New less-invasive treatments are likely to improve outcomes in elderly patients who previously have been considered at prohibitive risk for traditional procedures. Clinical trials enrolling elderly patients are limited and recommendations for management from younger patients frequently lack evidence-based support in patients aged >75 years.

Enfermedad cardiovascular en el anciano

Palabras clave:
Medicina geriátrica
Enfermedad coronaria
Estenosis de válvula aórtica
Ensayos clínicos

RESUMEN

El envejecimiento de la población en todo el mundo dará lugar a un número creciente de pacientes ancianos, en los que la cardiopatía es la principal causa de muerte. Las alteraciones de la fisiología cardiovascular con el envejecimiento normal y las comorbilidades causan diferencias en los problemas cardiacos y en la respuesta a los tratamientos en los pacientes ancianos. Los objetivos de la asistencia centrados en el paciente, como el mantenimiento de la independencia y la reducción de los síntomas, pueden ser más prioritarios que el aumento de la longevidad. Es probable que los nuevos tratamientos menos invasivos mejoren los resultados obtenidos en pacientes ancianos en los que antes se consideraba que el riesgo de los procedimientos tradicionales impedía su aplicación. Los ensayos clínicos en los que se ha incluido a pacientes ancianos son limitados y es frecuente que las recomendaciones de tratamiento basadas en pacientes de menor edad carezcan de respaldo en la evidencia para los pacientes de edad superior a 75 años.

Abbreviations

CHF: congestive heart failure
CHD: coronary heart disease
ICD: implantable cardioverter-defibrillator
NSTEACS: non- ST-elevation acute coronary syndrome
OMT: optimal medical therapy
PCI: percutaneous coronary intervention
STEMI: ST-elevation myocardial infarction
TAVI: transcatheter aortic valve implantation

INTRODUCTION

In 2000, 12% of the United States population was over 65 years old, with predicted growth to 20% by the year 2030; those more than 85 years of age constituted 27% of this older segment of the population.[1] The leading cause of death in those older than 65 years is heart disease, presenting challenges in diagnosis and treatment.[2] The care of elderly patients with cardiac conditions has many important differences from the care of younger patients with the same diagnoses. This article reviews some of the special considerations in the management of older patients with common cardiac conditions.

PHYSIOLOGY OF AGING

Vascular Physiology

Normal aging is associated with a decreased compliance of the central arteries due to a number of age-related changes in the

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structural components in the artery.[3,4] Older people have increased amounts of collagen in the arterial wall, and the collagen fibers have more permanent cross-linkages with other collagen fibers due to the nonenzymatic effects of advanced glycation end-products (AGE).[5] These AGE cross-links make the collagen resistant to routine breakdown and turnover. Age-related up-regulation of elastase results in lower levels of elastin in the central arteries, with consequent reduced elastic recoil and distensibility.[4] In addition to structural changes, the function of the endothelium of aged vessels is abnormal, with reduced production of nitric oxide (NO), resulting in decreased NO-dependent dilatation. Other molecular biology changes, including increases in specific matrix metalloproteinases, transforming growth factor-beta 1, and angiotensin II, also lead to endothelial dysfunction.[3,6]

Decreased vascular compliance and elasticity is commonly encountered in clinical practice as isolated systolic hypertension. The syndrome is characterized by increased systolic pressure, decreased diastolic pressure, and thereby a widened pulse pressure. Inability of the aged vessels to adequately absorb the energy of the pulsatile wave of systolic ejection of blood from the heart is then translated into kinetic energy by increasing the velocity of blood flow through the aorta and central arteries.[7,8] The faster blood velocity results in premature reflection of the pulsatile wavefront back to the heart, arriving during systole and increasing cardiac afterload. The normal reflection of the wave returning to the heart during diastole increases coronary flow. Loss of this coronary perfusion assistance combined with increased afterload can lead to myocardial ischemia in the elderly patient, even without severe atherosclerotic lesions, especially with increased myocardial oxygen demand, as with left ventricular hypertrophy (LVH), or decreased oxygen delivery capacity (as with anemia).

Cardiac Physiology

The hearts of aged individuals usually have increased mass.[9] Even in the absence of increased afterload, as with systemic arterial hypertension or aortic valve stenosis, concentric LVH is found.[10,11] There are decreased numbers of ventricular myocytes (due to apoptosis and necrosis), but the remaining myocytes enlarge. Myocyte hypertrophy may be from the increased afterload of arteriosclerosis, as above, or may relate to chronic exposure to stress. Fibroblast activity also affects the function of the older heart.[12] Fibroblasts beneficially remodel the ventricle, connecting the remaining myocytes to improve cardiac output, but excess fibrosis decreases the compliance of the ventricle and leads to dysfunction.

Stage 1 diastolic dysfunction (impaired relaxation) is a normal physiologic change of aging.[11] More advanced diastolic dysfunction may result in heart failure syndromes. Left ventricular ejection fraction (LVEF) remains unchanged with normal aging. Another frequent finding on imaging studies is the so-called "sigmoid septum" of the elderly, characterized by a sharp angulation between the ventricular septum and the aortic root, sometimes accompanied by accentuated local hypertrophy of the base of the intraventricular septum.[9] The ability of this structural change to cause obstruction to the left ventricular outflow tract has been debated. Although there is no resting gradient, under conditions of stress and low ventricular volume (eg, intravascular volume depletion) a gradient can develop, leading to symptoms of obstruction.

Aortic valve (AV) sclerosis is commonly encountered in elderly patients and is considered a normal consequence of aging; although AV leaflets are thickened, there is no obstruction to blood flow. The prevalence of AV sclerosis is up to 40% of those aged $\geq$75 years.[13] Because these sclerotic valves do not obstruct the left ventricular outflow, the presence of AV sclerosis itself is not considered pathologic. However, the finding of AV sclerosis on echocardiogram is a marker of increased risk of adverse cardiovascular outcomes.[14] AV sclerosis can progress to aortic valve stenosis (AS), but this is uncommon.[15]

An important concept in the physiology of cardiovascular aging is ventricular-vascular coupling. This theorizes that the increase in vascular and left ventricular stiffness combine to achieve stability in resting cardiac output at advanced age; however, these changes impair the ability of the cardiovascular system to accommodate to stress, ie, reduced cardiac reserve.[16–18] In older adults, cardiac output and index at rest are normal, but do not increase as significantly during exercise and stress as those of the younger patient, due to a variety of factors, including decreased beta-adrenergic responsiveness. The VO_{2max} decreases with normal aging due to decreased maximal cardiac output; decreased inotropy, lusotropy, and chronotropy; and decreased tissue extraction of oxygen.

Electrophysiology

The conduction system undergoes progressive fibrosis as the heart ages. In a 75-year-old, an estimated 10% of the original pacemaker cells in the sinus node remain functional.[9] Normal nodal degeneration and reduction in sympathetic and parasympathetic responsiveness result in lower resting heart rates in the elderly, as well as lower maximal heart rates achieved with exercise.[19]

Age Effects of Other Organ Systems

The renal system impacts most directly on the cardiovascular system with advanced age. As the kidneys age, their ability to excrete ingested sodium decreases, leading to sodium retention; changes in the renin-angiotensin-aldosterone system result in sodium reabsorption.[20] Thus, older patients are more sensitive to volume changes than their younger counterparts.[21] Decreases in the normal baroreceptor responsiveness result in more significant blood pressure fluctuations with postural changes.

Normative aging affects the cognition of elderly patients, even those without common problems such as dementia or mild cognitive impairment.[22] Normal age-related cognitive decline results in difficulty in memory, executive functioning, and processing speed, which can begin as early as the 30 s. The etiology of this syndrome is not known; postulates include oxidative stress, telomere shortening, and reduction in the immune system function. Patients with comorbid cardiac disease are at higher risk for age-related cognitive impairment.

Gait disturbances and immobility are very common in the elderly, up to 82% among those aged >85 years; as many as 50% of patients over 80 years of age have at least 1 fall per year.[23] Immobility and sedentary lifestyle exacerbate the physiologic effects of other systemic conditions; they result in decreased quality of life and exacerbate deconditioning, making falls more likely.[24] Risk of fall is increased with the use of psychotropic medications and neurologic disorders. Exercise training in the elderly is effective in improving functionality and quality of life while reducing risk of falls.

The overall accumulation of comorbid conditions and decrease of functionality and physiologic reserve is referred to as frailty.[25] Frailty involves the global reduction in ability to cope with physiologic stress and increases susceptibility to disease and death. Frail patients typically have unintentional weight loss

and poor mobility, but assessment for cognitive decline and severity of comorbid illnesses is also essential in evaluating frailty. Frailty is an important risk factor in prognostication and recommendations for management; frailty independently predicts the risk of loss of independence, disability, hospitalizations, and death.

Aging and Pharmacology

Altered pharmacokinetics and pharmacodynamics are characteristic in older patients. Decreased volume of distribution and creatinine clearance lead to significant changes in drug effect profiles and drug concentration. Much of the increased risk of adverse drug effects (such as bleeding associated with anticoagulants) in older adults can be attributed to medication overdosing. Renal impairment is often missed on routine laboratory studies because the decrease in muscle mass that accompanies normal aging leads to a lower serum creatinine level than in younger patients with the same level of kidney function.[26,27] All aged patients should have their glomerular filtration rate estimated by a formula such as the Cockcroft-Gault equation, and renally excreted drugs should be dosed accordingly.

Elderly patients are frequently on multiple prescription medications which should be carefully screened for interactions. As patients may see multiple providers, an accurate medication list must be maintained and verified at every encounter. Patients should be asked about over-the-counter medications and supplements, many of which have significant interactions with prescription drugs and with medical problems common in the elderly. Comorbid conditions may also increase the risk of adverse drug effects.

Goals of Care in the Elderly

In many of the randomized controlled trials that will be reviewed later, the primary outcomes include, and are sometimes limited to, prevention of mortality. Elderly patients may not view length of life as the highest priority. In fact, seniors more commonly report maintaining independence in daily living as their primary goal in the management of chronic illness.[28] Other goals important to the elderly include ability to ambulate, decreased hospitalizations, and decreased symptoms of illness (which may also be considered as prolongation of symptom-free life).[29] Common concerns of the elderly involve independence and the psychosocial and financial burdens of disease on themselves and their families. It is important to understand these motivations when discussing disease management with elderly patients and their families and to address specifically the impact of potential interventions on the quality of life measures important to the patient.

SPECIFIC CARDIOVASCULAR DISEASE STATES IN THE ELDERLY

Valvular Heart Disease

Aortic Valve Stenosis

In Europe, 56% of patients with AS are over 70 years old.[30] The vast majority have calcific degeneration of tricuspid aortic valves. Symptoms of AS (heart failure, angina, or syncope) portend a very poor prognosis unless definitive treatment is performed. Symptomatic patients with AS have traditionally been sent for surgical valve replacement if the risk-to-benefit ratio was favorable. Unfortunately, many patients of advanced age have significant comorbid conditions that place them at prohibitive surgical risk.[31,32] In the past decade, development of transcatheter aortic valve implantation (TAVI) for AS patients at prohibitive or very high surgical risk has shown great success in both Europe and the United States.[33–35] The Placement of Aortic Transcatheter Valves (PARTNER) study evaluated TAVI in two substudies: patients who were ineligible for surgical valve replacement (n = 358, mean age 83) and patients who were at high surgical risk (n = 699, mean age 84).[36] In patients who were inoperable, TAVI was superior to medical management [84% of medical management patients underwent balloon aortic valvuloplasty (BAV) for symptom control] in the primary end point of all-cause mortality at 1 year (30.7% versus 50.7%, $P < .001$), although there was a higher incidence of stroke and vascular complications in the TAVI group. New York Heart Association (NYHA) functional class was significantly better in the TAVI group (74.8% NYHA I or II versus 42%, $P < .001$). Subgroup analysis showed benefit in patients aged 85 and younger as well as >85 years. In the substudy of high surgical risk, patients were randomized to surgical valve replacement or TAVI. There was no significant difference in mortality at 1 year (26.8% versus 24.2%, $P = .62$); NYHA class was also similar at 1 year [presented, 60th Scientific Sessions of the American College of Cardiology, New Orleans, Louisiana, United States, April 3, 2011]. There were significantly more strokes/transient ischemic attacks in the TAVI group (8.3% versus 4.3%, $P = .04$). Again, subgroup analysis showed similar findings in those aged 85 and younger and those over 85 years.

Symptomatic AS requires a mechanical intervention for effective treatment. Medical therapy (with BAV) is not an effective option for durable symptom relief or mortality. In patients who are not surgical candidates, TAVI is the best available treatment. In patients at high surgical risk, valve replacement at an expert center appears to be the best option, as stroke risk with TAVI is unacceptably high. As newer transcatheter valves are developed and implantation techniques improve, this observation may change.

Elderly patients with "asymptomatic" aortic stenosis which appears severe by echocardiography should be carefully questioned to determine if they are truly without symptoms. Patients with a sedentary lifestyle may not perceive symptoms due to their lack of activity. Patients with disparity between measured AS severity and symptoms can undergo careful symptom-limited exercise testing to evaluate for masked or undetected exercise intolerance.[37] Patients who develop symptoms or ECG changes at low levels of activity should have close monitoring with a low threshold to consider valve replacement. In patients who are not candidates for surgery or TAVI, BAV remains an option for short-term symptom relief, or as a bridge to a more permanent solution.

Mitral Valve Disease

The next most common indication for valvular surgery in the elderly is mitral regurgitation (MR), with recommendations for replacement or repair of severe asymptomatic or symptomatic MR the same as in younger patients.[21,28,38] Preference is for mitral valve repair as this maintains the geometry of the valve and ventricle, which is thought to preserve left ventricular function. Mitral valve surgery in elderly patients, performed through a sternotomy, has a mortality in case-control series of about 9%.[39,40] Less invasive techniques of a lateral thoractomy should be considered when mitral repair is felt to be achievable;

better outcomes were evident in a meta-analysis of 1 randomized controlled trial and 10 case-control series.[41] The even less invasive transcatheter mitral valve clipping has been used in recent clinical trials, but is not approved for widespread clinical use in the United States.[42,43] In the Endovascular Valve Edge-to-Edge Repair Study II (EVEREST II), 279 patients (20% older than 75 years) with 3+ or 4+ MR were randomized to percutaneous closure or open mitral valve repair; the primary end point was a composite of mortality, freedom from mitral valve surgery, and freedom from 3+ or 4+ MR.[44] At 12 months, surgical repair was superior (73% versus 55%, $P = .007$), which was predominantly due to the 20% of percutaneously treated patients who required later mitral surgery. In post-hoc analysis, patients aged >70 years had equivalent efficacy when treated percutaneously versus surgically. The safety outcome of occurrence of any major adverse event (including requirement for blood transfusion) was better in the percutaneous group (15% versus 48%, $P < .001$), but this difference became nonsignificant when transfusion was not included.

Rheumatic heart disease is rapidly decreasing in industrialized countries; however, elderly patients are one subgroup of the population with a relatively high prevalence of rheumatic heart disease.[38] Most of these patients already have the diagnosis and many will have undergone mitral valve replacement or commissurotomy. A majority also have atrial fibrillation and require long-term anticoagulation for embolic prevention. Patients with rheumatic mitral stenosis and relatively low amounts of valve calcification and with little mitral regurgitation can be considered for balloon valvuloplasty.[37]

Coronary Heart Disease

Prevention of Coronary Heart Disease

Coronary heart disease (CHD) is the leading cause of death of elderly men and women: 81% of adults who die of CHD are aged 65 or older.[2] Risk factors for CHD in the elderly are the same as in younger patients, including diabetes, hypertension, tobacco smoking, dyslipidemia, obesity, family history, and physical inactivity. The best strategies for prevention of CHD in the elderly have been much debated, given the low numbers of elderly patients in most prevention clinical trials.

Hypertension. Hypertension in the elderly was once considered a necessary physiologic compensation for age-related vascular changes. However, trials on hypertension treatment in the elderly demonstrate that blood pressure control leads to significant reductions in clinical end points of myocardial infarction, stroke, and cardiovascular death. In the Systolic Hypertension in the Elderly Program (SHEP), over 4000 patients (mean age 72) with stage II hypertension were randomized to placebo or hypertensive management.[45] Patients treated to achieve an average systolic blood pressure of 143 mmHg had a 36% relative risk reduction in stroke ($P = .0003$) at 4.5 years. In the Hypertension in the Very Elderly Trial (HYVET), a randomized, placebo-controlled study of patients aged 80 years and older, the 21% relative risk reduction in overall mortality at 2 years ($P = .02$) prompted the trial to be stopped prematurely.[46] The HYVET blood pressure target was < 150/80 mmHg.

Both trials above used a diuretic as initial therapy with the addition of atenolol (in SHEP) or perindopril (in HYVET) if needed to achieve the blood pressure goal. The 2003 Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure recommends that initial therapy for hypertension should be a diuretic unless a comorbid condition suggests another medicine is preferable [such as angiotensin-converting enzyme-inhibitors (ACE-I) for diabetes].[47] Recommendations from the American College of Cardiology/American Heart Association (ACC/AHA) are a blood pressure goal of <140/90 mmHg in patients aged 65-79 years and a systolic blood pressure goal of <145 mmHg in those 80 years and older [embargoed for publication, May 17, 2011, *Journal of the American College of Cardiology*]. In the elderly a "start low, go slow" titration strategy should be used given the higher risk for medication side effects and interactions.

Dyslipidemia. Although many elderly patients have an abnormal lipid profile and comorbid conditions associated with dyslipidemia (CHD, stroke, and peripheral artery disease), the trial data on the treatment of elderly patients with the most common potent medications, 3-hydroxy-3-methyl-glutaryl-CoA reductase inhibitors (statins), is relatively sparse. The one large, randomized trial dedicated to statin treatment in the elderly was the Prospective Study of Pravastatin in the Elderly at Risk (PROSPER) trial, which enrolled almost 6000 patients aged 72-80 years. There was significant absolute risk reduction (2.1%, $P = .014$) in the composite end point of CHD death, stroke, and nonfatal myocardial infarction (MI), although subgroup analysis showed that the greatest benefit was secondary prevention in patients with existing CHD, and not primary prevention in those with cardiovascular risk factors.[48] There was no significant difference in the secondary end point of all-cause mortality. Another large clinical trial of statins in patients with diabetes or known vascular/cardiovascular disease, the Heart Protection Study (HPS), was not designed specifically to evaluate the elderly, but post-hoc analysis of the subgroup aged 75-80 year had a 9% absolute risk reduction in major vascular events associated with use of simvastatin ($P = .0002$).[49]

The Treating to New Targets (TNT) trial evaluated the impact of intensive lipid-lowering therapy, randomizing 10 000 patients aged 75 and younger with CHD to 10 mg or 80 mg of atorvastatin and following them for 5 years. Post-hoc analysis of 3800 TNT patients aged 65 and older found that the primary end point of first major cardiovascular event (cardiac death, MI, or stroke) was significantly reduced in the 80 mg group (10.3% versus 12.6%, $P = .032$). The low-density lipoprotein (LDL) level reached by the 80 mg dose was 72 mg/dl versus 97 mg/dl in the 10 mg group, supporting the efficacy of an intensive treatment goal in elderly patients.[50]

The Justification for Use of Statins in Prevention: An Intervention Trial Evaluating Rosuvastatin (JUPITER) study was a primary prevention trial in patients without CHD or CHD risk equivalents, but elevated C-reactive protein levels and LDL values <130 mg/dl.[51] A secondary analysis of the cohort of patients aged >70 years at enrollment found that these patients accounted for less than a third of the total study population, but accrued almost half of the primary end points.[52] The elderly patients had even greater benefit from rosuvastatin than patients aged <70 years, with an absolute risk reduction of the primary end point of 0.77 compared to 0.52 events per 100 person-years ($P < .001$).

The current National Cholesterol Education Program (NCEP) Adult Treatment Panel (ATP-III) guidelines recommend treatment of LDL cholesterol to a goal of <100 mg/dl in patients with known CHD, or with CHD risk equivalents, such as diabetes mellitus, with the option of the more aggressive target of <70 mg/dl in patients at higher risk.[53]

Symptomatic Coronary Heart Disease Syndromes

In the elderly, CHD symptoms are more difficult to detect than in younger patients for a variety of reasons. Elderly patients

frequently have a more sedentary lifestyle and may not have exertional symptoms. Although chest discomfort remains the most frequent presenting complaint of patients with CHD, the elderly have a higher percentage of atypical chest pain complaints as well as nonchest pain presentations (general fatigue/malaise, dyspnea, abdominal pain, nausea and vomiting, or syncope).

Stable Angina

Treatment of chronic stable angina has become a debated topic in recent years, prompted by the Clinical Outcomes Utilizing Revascularization and Aggressive Drug Evaluation (COURAGE) trial which showed no significant difference in major cardiac events between groups treated with optimal medical therapy (OMT) and those treated with percutaneous coronary intervention (PCI) added to OMT.[54] In a prespecified subset analysis of the 904 patients older than 65 years, there was no difference in outcomes of major cardiac events or angina-free rates between the OMT and OMT + PCI groups.[55] These data are supported by results of the Randomized Trial of Invasive Versus Medical Therapy in Elderly Patients (TIME) study which demonstrated no difference in quality of life or survival of patients with stable angina treated with PCI versus OMT.[56] These are the only contemporary randomized trials of treatment of stable angina in older patients and suggest that much of the long-term benefit of treatment of angina in older adults derives from the appropriate use of OMT. For chronic stable angina, OMT consists of antiplatelet therapy, lipid-lowering drugs, and antihypertensive and anti-anginal medications, which are discussed below.

Antiplatelet Therapy. The powerful role of aspirin in both primary and secondary prevention of CHD was confirmed by a meta-analysis which showed a significant reduction in cardiovascular death, MI, and stroke in patients with cardiovascular disease receiving aspirin therapy, including elderly patients.[57] Current ACC/AHA guidelines recommend 75-162 mg of aspirin daily in patients with chronic stable angina, unless contraindicated.[58] Patients who are aspirin allergic should be considered for thienopyridine therapy.

Beta-Blockers. Beta-blockers have a class I indication in patients with chronic angina.[58] The anti-anginal action of beta-blockers derives from a combination of their negative chronotropic and inotropic effects.[59] The reduction of resting heart rate and blunting of the heart rate response to physiologic stress reduces myocardial oxygen demand below the level that produces ischemia. The prolongation of diastole improves coronary perfusion and reducing myocardial contractility also reduces ischemia.

Beta-blockers must be used with caution in elderly patients, especially those with known or suspected conduction system disease, as they may precipitate higher-grade AV block. Beta-blockers are contraindicated in patients with high-grade AV block or sinus node dysfunction who do not have electronic pacemakers. In patients with severe obstructive airway disease (asthma or chronic obstructive pulmonary disease), beta-blockers must be initiated carefully, with preference for agents with beta-1 receptor blockade selectivity (such as metoprolol or bisoprolol) to avoid precipitation of bronchoconstriction. Atenolol, a beta-1 selective agent, is excreted by the kidney and is not recommended in older patients who have reduced glomerular filtration rates.

Renin-Angiotensin-Aldosterone System Blockers. Although ACE-I do not have a direct effect on anginal symptoms except by lowering afterload, which reduces myocardial work, they have significant benefit in patients with chronic CHD. The Heart Outcomes Prevention Evaluation (HOPE) trial randomized patients with diagnosed CHD, peripheral artery disease, or stroke, or with diabetes mellitus plus one other risk factor for CHD, to treatment with ramipril versus placebo.[60] In 2755 HOPE patients aged 70 and older (58.1% with stable angina), patients receiving ramipril had significantly lower rates of cardiovascular death [hazard ratio (HR) = 0.71, $P = .003$], myocardial infarction (HR = 0.75, $P = .006$) and stroke (HR = 0.69, $P = .013$).[61] In the European Trial on Reduction of Cardiac Events with Perindopril in Patients with Stable Coronary Artery Disease (EUROPA) study, 31% of the 12 000 patients were over age 65; perindopril was associated with a 20% relative risk reduction ($P = .0003$) in the combined primary end point of cardiovascular death, MI, or cardiac arrest.[62] Importantly, though, 81% of EUROPA patients had no angina at enrollment.

The third major study evaluating ACE-I in stable CHD without congestive heart failure (CHF) is the Prevention of Events with Angiotensin Converting Enzyme Inhibition (PEACE) trial, whose results contradicted the prior studies.[63] The PEACE trial enrolled 8290 patients (average age 64, with 11% > age 75) with chronic CHD and randomized them to trandolapril versus placebo. The combined end point of cardiac death, MI, or revascularization was not significantly different between the two groups. These trials were combined in a meta-analysis which found that ACE-I use significantly reduced all-cause mortality, cardiovascular mortality, nonfatal MI, and stroke (10.7% versus 12.8%, odds ratio of 0.82, $P < .0001$).[64]

The updated ACC/AHA guidelines for management of stable CHD have a class I recommendation that ACE-I (or angiotensin II receptor blockers [ARB-II], in ACE-I intolerant patients) be started in stable CHD patients at intermediate or high risk (eg, uncontrolled risk factors or not revascularized) with a class IIA recommendation for these agents in lower-risk patients.[58] There is a clear indication for ACE-I in patients with LVEF of 40% or less and those with comorbid hypertension, diabetes, or chronic kidney disease.

Nitrates, Calcium-Channel Blockers, and Other Anti-Anginal Drugs. Nitrates and calcium-channel blockers (CCB) are indicated for the relief of angina in patients with CHD, but do not provide survival benefit.[59] Nitroglycerin administered sublingually has a rapid onset of action, around 1 to 3 min, and has been in effective clinical use since 1878. Long-acting formulations such as isosorbide mono- or dinitrate are commonly prescribed for patients with chronic angina. They are less effective at relieving angina than sublingual nitroglycerin and can result in the development of tolerance, which can occur as soon as after 12 h of use. The CCBs treat angina by coronary vasodilation as well as some negative inotropy. The dihydropyridine (DHP) CCBs (such as amlodipine, nifedipine, and felodipine) are more selective agents with fewer negative inotropic effects than the non-DHP (verapamil and diltiazem). Non-DHP CCBs also have a significant negative chronotropic effect. Because of their negative inotropic effects, non-DHP CCBs are contraindicated after large MIs and in patients with reduced LVEF.[65] DHPs appear safe in patients with reduced LVEF.[66] Short-acting nifedipine should be avoided, but long-acting nifedipine is safe and effective in relieving angina in patients with hypertension.[67,68] A novel anti-anginal agent, ranolazine, reduced angina without hemodynamic compromise.[69] Subgroup analysis of elderly patients in ranolazine clinical trials showed similar efficacy to younger patients with no difference in serious adverse events.[70]

Unstable Angina/Non-ST-Elevation Myocardial Infarction

Although patients aged 75 and older account for 32% to 38% of non-ST-elevation acute coronary syndromes (NSTEACS) in registries, they comprise only 18% of the study population in clinical trials.[71] Elderly patients are at higher risk for complications of both the NSTEACS event and the therapeutic interventions. The paucity of evidence for the management of NSTEACS in the elderly has resulted in significant age-based disparities.

Antiplatelet Therapy (Oral). Aspirin is a cornerstone of antiplatelet management of chronic CHD and acute presentations. Aspirin use in the elderly during the presentation of acute MI and chronically thereafter markedly reduced vascular events and death.[57] Clopidogrel is also effective as an adjunct antiplatelet agent. The Clopidogrel in Unstable Angina to Prevent Recurrent Ischemic Events (CURE) trial subanalysis of patients aged 65 and older showed a 2% absolute risk reduction in nonfatal MI, cardiac death, and stroke, similar to the effect in younger patients.[72] A combination of aspirin and clopidogrel is recommended for patients (including the elderly) at high risk.[73] When dual antiplatelet therapy is used, aspirin doses of 75 to 150 mg are as effective as higher doses with better safety in terms of gastrointestinal bleeding.[57,74] The newest currently available oral antiplatelet, prasugrel, is effective in reducing rates of cardiac death, MI, or stroke, but is associated with increased bleeding compared to clopidogrel.[75] Patients aged 75 and older had less clinical benefit from prasugrel in post-hoc analysis; more clinical trial data is needed before prasugrel can be recommended for this population.

Antiplatelet Therapy (Intravenous). Glycoprotein (GP)IIb/IIIa inhibitors are the only intravenous antiplatelet agents commercially available in the United States. The two small-molecule GPIIb/IIIa antagonists are tirofiban and eptifibatide, both with indications for the treatment of NSTEACS.[73] The most recent randomized clinical trial using tirofiban in NSTEACS, the Platelet Receptor Inhibition in Ischemic Syndrome Management in Patients Limited by Unstable Signs and Symptoms (PRISM-PLUS) study, showed significant benefit at 7 days with a combination of heparin and tirofiban compared to either agent alone.[76] This reduction in death, MI, and ischemia was demonstrated in older as well as younger patients. The first trial investigating eptifibatide in NSTEACS patients, the Platelet Glycoprotein IIb/IIIa in Unstable Angina: Receptor Supression Using Integrilin Therapy (PURSUIT) study, showed a significant reduction in death and MI in the entire study population, but benefit was not seen in patients aged 65 and older.[77] In follow-up subgroup analysis, patients aged 60 to 79 years had significant reductions in death and MI, but patients aged 80 and older had higher rates of death and MI at 30 days, as well as higher risk of bleeding.[78] A meta-analysis of GPIIb/IIIa trials showed a trend toward decreased benefit in aged patients, with patients older than 59 years having no significant benefit.[79] Most recently, the Early Glycoprotein IIb/IIIa Inhibition in Non-ST-Segment Elevation Acute Coronary Syndrome (EARLY-ACS) trial randomized patients to eptifibatide ''upstream'' (12 or more hours prior to angiography) or placebo, with provisional use of eptifibatide after angiography (''downstream'').[80] The outcome of death, MI, or revascularization was not significantly different between upstream and downstream use of eptifibatide in the entire population, nor in the subgroup aged 75 and older. The Acute Catheterization and Urgent Intervention Triage Strategy (ACUITY) trial evaluated the use of GPIIb/IIIa inhibitors plus either heparin or bivalirudin versus bivalirudin alone in patients with NSTEACS who were invasively managed.[81] This trial failed to show a benefit of any of these strategies for death, MI, or revascularization but a significant reduction in bleeding risk in the group receiving bivalirudin alone. A prespecified subgroup analysis in patients aged 75 and older showed similar outcomes to the overall study, with no change in risk for the ischemic end point and with an even greater absolute reduction in bleeding events (3.1% absolute risk reduction in major bleeding, $P < .05$) compared to younger patients.[82]

Review of the literature of upstream GPIIb/IIIa use in elderly patients showed the overall benefit to be small or equivocal with no significant difference in outcomes with upstream compared to downstream use.[83] There is a substantial increased risk of bleeding associated with their use in older patients compared to heparin or bivalirudin alone. As the potential benefits of GPIIb/IIIa inhibition were principally demonstrated in patients undergoing an invasive strategy, they should not be used in elderly patients undergoing a conservative/noninvasive strategy. Adjusted dosing is necessary based on weight and renal function; bleeding risk in elderly patients is frequently increased to an even greater degree due to inadvertent overdosing.

Antithrombotic Therapy. Heparin has long been a mainstay of the acute treatment for acute MI and unstable angina. In the past two decades, trials comparing low-molecular weight heparins (LMWHs) with unfractionated heparin (UFH) have had inconsistent results.[71] There is no clear favorability of one agent over the other. As with GPIIb/IIIa inhibitors, attention must be paid to dosing guidelines based on weight and renal function. Fondaparinux, a factor Xa inhibitor, has been compared to enoxaparin, a LMWH, in NSTEACS patients; it failed to show significant benefit in older patients in the combined cardiac event end point, but had a significant reduction in bleeding.[84] More trial data are needed before fondaparinux can be recommended for routine clinical use in elderly patients.

In NSTEACS patients undergoing an invasive strategy, bivalirudin is an excellent treatment option.[81,82] The results from the ACUITY trial showed that bivalirudin has similar effects for ischemic outcomes but is superior in terms of bleeding risk, which is of great concern in the elderly patient. For this reason, in many centers bivalirudin has become a highly utilized agent for anticoagulation in elderly patients undergoing coronary angiography and revascularization.

Early Invasive Versus Conservative Management. The most important decision in management of NSTEACS in elderly patients regards invasive coronary angiography. Early trials appeared to favor an initially conservative approach in older patients; however, more recent trials (with more widespread use of modern therapies such as clopidogrel and coronary stenting) have shown benefit in an early invasive strategy in select patients.[73] Two recent large trials compare strategies in NSTEACS patients. In the Treat Angina with Aggrastat and Determine Cost of Therapy with an Invasive or Conservative Strategy – Thrombolysis in Myocardial Infarction (TACTICS-TIMI 18) trial, 2220 patients (mean age 62, 44% aged 65 and older) received aspirin, heparin and tirofiban and were randomized to initial noninvasive compared to early invasive strategies.[85] Early invasive strategy patients had angiography within 48 h of randomization. Patients in the conservative treatment arm only underwent angiography if there were high risk features on stress testing, recurrent severe ischemia during the initial hospitalization, or documented ischemia in follow-up. Overall, 98% of the invasive strategy patients underwent coronary angiography and 64% underwent revascularization either during the initial

hospitalization or during the 6-month follow-up period, compared with 61% of conservative strategy patients who underwent catheterization and 45% who underwent revascularization. The composite end point of death, MI, or hospitalization for acute coronary syndrome at 6 months was significantly lower in the invasive strategy group compared to the initially conservative strategy (15.9% versus 19.4%, $P = .025$). Benefit of early invasive strategy was primarily in patients with intermediate or high TIMI risk scores and those with abnormal troponin levels. In a subgroup analysis, patients aged 75 and older managed invasively had an even greater absolute risk reduction than younger patients (10.8% versus 21.6%, $P = .02$). A higher risk of bleeding was seen in invasively managed older patients (16.6% versus 6.5%, $P = .009$).

The Invasive Versus Conservative Treatment in Unstable Coronary Syndromes (ICTUS) study randomized 1200 patients to either angiography within 48 h in addition to intensive medical treatment (which included aspirin and enoxaparin per the study protocol, with encouraged use of clopidogrel) compared to medical therapy alone, followed by a predischarge exercise test.[86] In the conservative or "selectively invasive" strategy group, patients were sent for angiography only if they had refractory ischemia or instability, or if stress testing revealed significant ischemia. At 1-year follow-up, 99% of the invasive group had undergone angiography and 79% revascularization, compared to 67% and 54% in the selective strategy group. There was a difference in medical therapy between the groups, with 61% of the early invasive arm prescribed clopidogrel at discharge versus 49% of the selectively invasive arm. Results at 1 year showed no significant difference in the primary outcome of death, MI, or rehospitalization. This lack of significant difference was seen in the older subpopulation as well. In a 2010 meta-analysis of these two trials plus the earlier Fragmin and Fast Revascularization During Instability in Coronary Artery Disease (FRISC-II) trial, there was a very significant benefit (in death or MI) to a routinely invasive strategy in high-risk patients, and a lesser but still statistically significant benefit in intermediate-risk patients at 5-year follow-up.[87] These prospective randomized studies, as well as observational data on revascularization in elderly NSTEACS patients, support the ACC/AHA recommendation that patients with indicators of high risk of poor outcomes (including the elderly) as estimated by risk scores, such as the TIMI or Global Registry of Acute Coronary Events (GRACE) risk scores, should undergo an early invasive strategy unless such a strategy is contraindicated.[73] Despite these recommendations and the findings that elderly patients are both at highest risk of poor outcomes and receive the highest absolute risk reduction by invasive management, there remains a significant disparity between younger and older patients referred to angiography and revascularization.

ST-Elevation Myocardial Infarction

Fibrinolytic Therapy. Many trials establishing fibrinolytic therapy for ST-elevation myocardial infarction (STEMI) had few or no patients over the age of 75; however, meta-analysis of fibrinolytic trials led to the conclusion that, in the absence of known contraindications, fibrinolytics are effective in older patients.[88] One analysis of elderly patients (75 or older) in thrombolytic trials for STEMI showed a 15% relative mortality reduction ($P = .03$).[89,90] Because many elderly patients present to facilities without emergent PCI capabilities, the documented efficacy of fibrinolysis in the elderly is useful in determining treatment strategy, as will be discussed later.

The indications for fibrinolysis in elderly patients with STEMI are the same as for younger patients; however, elderly patients are more likely to have contraindications to fibrinolytics.[91] The most devastating complication of thrombolytic therapy is intracranial hemorrhage (ICH). Although the incidence of ICH increases in older patients, the rate remains low even among the very old (2.9% in patients over age 85).[92] The choice of fibrinolytic agent in older patients may be important, with tenecteplase having significantly less ICH compared to tissue plasminogen activator in one trial, although neither was superior in cardiac outcomes.[93] The use of adjunctive heparin appears to affect ICH rates. In initial studies, enoxaparin, a LMWH, was associated with an improved clinical benefit compared to heparin, but with significantly increased risk of ICH, the majority in patients over age 75.[94] It was hypothesized that this was due to overdosing of these patients since the enxoparin dose was not adjusted for age or renal function. Subsequent study showed no increased rates of ICH when enoxaparin was dosed at 0.75 mg/kg every 12 h, without an initial intravenous bolus. The primary outcome of death or MI was superior in the group receiving LMWH compared with UFH as adjunctive therapy (9.9% versus 12%, $P < .001$), although the risk of major bleeding was increased (2.1% versus 1.4%, $P < .001$).[95]

Percutaneous Coronary Intervention. Since major bleeding and ICH are the principal concerns of thrombolytic use in the elderly and an invasive strategy in NSTEACS appears superior in high-risk patients, there is a presumed advantage of primary PCI compared to fibrinolysis in elderly adults with STEMI. This assumption has rarely been tested in randomized clinical trials with large numbers of elderly patients, but the data that exist are supportive.[88] One randomized clinical trial of therapy for STEMI in patients over the age of 75 was performed by the Zwolle Myocardial Infarction Study Group.[96] Patients without contraindications to fibrinolysis were randomized to primary PCI or streptokinase. Enrollment in the trial was stopped prematurely due to safety monitoring which demonstrated a large significant difference in outcomes favoring primary PCI. Despite enrolling only 87 patients, an absolute risk reduction (of the composite end point of death, MI, or stroke) of 20% ($P = .01$) was seen at 30 days in patients undergoing PCI versus streptokinase infusion. The investigators of the Primary Coronary Angioplasty Trialists (PCAT) group pooled data from 11 randomized trials, in which 640 patients were 70 or older, and found a significant mortality benefit in primary PCI over thrombolytics at 30 days (13.3% versus 23.6%, $P < .05$).[97] A second PCAT analysis of 22 trials found that older patients benefit more from primary PCI than relatively younger patients, with an absolute mortality reduction of 6.9% in patients aged 85 or older compared to a 1% reduction in those younger than 65.[88,98] Based on these findings, elderly patients presenting with STEMI of recent onset should be preferentially treated with primary PCI unless there will be significant delay in angiography/PCI, in which case fibrinolysis should be performed unless contraindicated.

Arrhythmias

Atrial Fibrillation

Atrial fibrillation is the most common clinically significant arrhythmia in the elderly and the incidence of atrial fibrillation increases with age.[99] In treating atrial fibrillation the two most important issues are rate-control versus rhythm-control strategies and anti-coagulation.

Rate Control Versus Rhythm Control. Nine large, randomized, controlled trials have compared pharmacologic rate-control and rhythm-control strategies. Four of these trials have been combined in a meta-analysis of over 5000 patients, although 4060 patients were enrolled in a single trial, the Atrial Fibrillation Follow-up Investigation of Rhythm Management (AFFIRM) study.[100,101] Since the results of the meta-analysis closely matched the results of the AFFIRM trial, we will discuss AFFIRM alone in more detail. The AFFIRM investigators randomized patients to either rhythm-control, with an antiarrhythmic agent chosen by the treating physician, or rate-control, with the rate-controlling agent chosen by the treating physician. Rate-control targets were 80 bpm at rest and 110 bpm during a 6-min walk. Anticoagulation was required in the rate-control group, and was encouraged in the rhythm-control group; 85% of rate-control patients and 70% of rhythm-control patients were treated with warfarin. After a mean follow-up of 3.5 years, there was no significant difference in mortality between the rate- and rhythm-control groups; however, hospitalization rates and adverse drug events were higher in the rhythm-control group.[100] A pre-defined subgroup analysis found a statistically significant increased hazard of death in patients aged 65 and older undergoing rhythm-control treatment. Rate control also appeared superior in patients with CHD and those without CHF.

In patients with CHF and atrial fibrillation, the Atrial Fibrillation and Congestive Heart Failure trial found that in patients with LVEF of 35% or less, symptomatic CHF, and atrial fibrillation there was no significant difference in the primary outcome of cardiac death (27% in the rhythm-control group versus 25% in the rate-control group, $P = .59$).[102] Although an elderly subgroup analysis was not reported, the investigators stated that no significant difference in outcomes was seen in any subgroup.

The intensity of rate control is a frequently raised question and was addressed by the Rate Control Efficacy in Permanent Atrial Fibrillation: a Comparison Between Lenient Versus Strict Rate Control II (RACE II) trial.[103] The RACE II investigators found that lenient rate control (resting heart rate goal of less than 110 bpm) had a noninferior outcome at 3-year follow-up compared to patients undergoing strict rate control (goal heart rate < 80 bpm at rest and <110 bpm with exercise). They also found that lenient control was easier to achieve and that symptoms of atrial fibrillation and NYHA class were similar between the two groups.

In the past decade, catheter ablation techniques have become widespread; however, the data regarding the use of catheter ablation in the older patient is sparse.[104] In several small, mostly retrospective, studies of atrial fibrillation ablation in elderly patients, the procedure was generally safe and efficacious, with success rates similar to those in younger patients. More randomized prospective data are needed before ablation can be widely recommended for elderly patients.

A strategy of lenient rate control seems most appropriate for the general management of atrial fibrillation in the elderly. When patients remain severely symptomatic from paroxysms of atrial fibrillation, initiation of antiarrhythmic therapy is reasonable, with the understanding that this strategy does not eliminate the need of appropriate anticoagulation for stroke prevention.

Anticoagulation. Age is an independent risk factor for stroke in patients with atrial fibrillation, with the risk of stroke increasing 1.4-fold per decade.[105] Despite this, appropriate anticoagulation is underprescribed in elderly patients with atrial fibrillation. The decision on stroke prevention strategy is complicated, and risk scoring systems have been developed to aid physicians in decision making. The most popular risk score in the United States, the $CHADS_2$ score (an acronym for CHF, Hypertension, Age >75, Diabetes Mellitus, and Prior Stroke or Transient Ischemic Attack), incorporates age and comorbid conditions to estimate stroke risk in patients with nonvalvular atrial fibrillation.[106,107] Common practice is to prescribe warfarin for patients with $CHADS_2$ scores of 2 or greater, and to use aspirin for patients with lower scores.[108] Because of their high incidence of comorbid conditions, most elderly patients are in the higher risk category and therefore have indication for warfarin anticoagulation. Many physicians are reluctant to prescribe warfarin therapy in older patients, because of concerns of bleeding and ICH.[109] A review of 472 patients (mean age 77) initiated on warfarin therapy for atrial fibrillation found that 26% of patients aged 80 or older had warfarin therapy discontinued at 1 year, mostly because of safety concerns.[110] In this retrospective cohort, the rate of major hemorrhage in patients aged 80 and older was 13.1 per 100 person-years, compared to 4.7 in patients under age 80 ($P = .009$). Risk of hemorrhage was dramatically increased in patients with international normalized ratio (INR) of 4 or higher and in patients with $CHADS_2$ scores of 3 or greater. This simultaneous increase in the risk of bleeding and stroke creates a therapeutic dilemma that was addressed by the Birmingham Atrial Fibrillation Treatment of the Aged (BAFTA) trial, which randomized 973 patients aged 75 and older to aspirin (75 mg per day) or warfarin (INR goal of 2-3).[111] The primary outcome was a composite of the catastrophic events discussed above – stroke, ICH, or arterial embolism. The primary end point occurred in 1.8% of patients on warfarin therapy compared to 3.8% of patients on aspirin therapy ($P = .003$). There was no significant difference in rates of extracranial hemorrhage between the groups. Based on this information, the overall risk-to-benefit ratio of warfarin anticoagulation in elderly patients with atrial fibrillation favors the therapy; however, the decision remains complicated and individual patient factors, such as fall risk and medication compliance, play an important role. When the decision is made for warfarin anticoagulation, close monitoring of INR values is recommended.[109]

A new oral agent for anticoagulation in atrial fibrillation recently approved in the United States is dabigatran, an oral direct thrombin inhibitor. In the Randomized Evaluation of Long-Term Anticoagulation Therapy (RE-LY) trial, 18 113 patients were randomized to either warfarin (INR goal of 2-3) or dabigatran 110 mg or 150 mg twice daily and followed for 2 years.[112] In the primary outcome of stroke or systemic embolism, dabigatran 150 mg was superior to warfarin (1.11% versus 1.69%, $P < .001$) and dabigatran 110 mg was noninferior to warfarin (1.53%, $P < .001$). The rates of major bleeding were 3.36% in the warfarin group compared to 2.71% in the dabigatran 110 mg group ($P = .003$) and 3.11% in the dabigatran 150 mg group ($P = .31$). These outcomes are encouraging as they address both efficacy of stroke prevention and risk of major bleeding and the results appear applicable to most older adults; the average age of the study population was 72. However, dabigatran is primarily renally cleared, and patients with significant renal dysfunction were excluded from the trial.[113] Although the differences in end points were statistically significant, the clinical significance is modest, as the number needed to treat with dabigatran 110 mg to prevent 1 major bleeding episode at 2 years is 153. The agent seems to have a role in patients for whom maintaining the INR in the desired therapeutic range has been historically difficult or who have high stroke risk but have had significant bleeding events on warfarin. As more experience with dabigatran is

acquired, its role in anticoagulation in the elderly will become clearer.

Ventricular Arrhythmias and Sudden Cardiac Death

Secondary Prevention. Trials evaluating the treatment of patients with symptomatic ventricular arrhythmias, including sudden cardiac death (SCD), have demonstrated conclusively that implantable cardioverter-defibrillators (ICDs) are superior to antiarrhythmic therapy for the prevention of mortality.[114–117] There is less data on secondary prevention of SCD in the elderly. A meta-analysis of 3 secondary prevention trials, enrolling 1866 patients (252 were 75 or older), found that ICD implantation did not reduce all-cause death or arrhythmic death in patients aged 75 and older.[118] This finding does not countermand the current guidelines for ICD implantation for secondary prevention of SCD. However, careful consideration should be given other life-limiting conditions or contraindications to ICD implantation since efficacy at older ages has not been conclusively demonstrated.[119]

Primary Prevention. Primary prevention trials have shown a mortality benefit in patients undergoing ICD implantation with reduced LVEF.[120–126] However, similar to the secondary prevention trials, many subgroup analyses have failed to show benefit in older patients. Only one prospective trial's subgroup analysis showed a benefit to ICD implantation in elderly patients, the Multicenter Automatic Defibrillator Implantation Trial II (MADIT II). In this study, patients with prior MI and a LVEF of 30% or lower were randomized to medical therapy or ICD implantation.[122] Patients aged 70 and older (a predefined subpopulation of 436) benefitted from ICD implantation. A post-hoc analysis of MADIT II patients aged 75 and older (n = 204) found a nonsignificant benefit from ICD implantation (HR 0.56, 95% CI 0.29-1.08, $P = .08$).[127] An observational study of Medicare patients in the United States showed a significant benefit to ICD implantation in senior citizens, mean age 76 years.[128]

In the ACC/AHA guidelines for ICD implantation, age is not mentioned specifically. However, the benefit of ICDs is not seen until 1 year post-implantation, and guidelines recommend implantation only in patients with the expectation of 1 year of survival with good functional status.[119] Patients with life expectancy of less than a year or with severe comorbid conditions should not have ICDs implanted. Although many elderly patients may have indications for ICD implantation and no clear contraindications, the impact of the implantation of an ICD on both the length of life and the quality of living and dying must be established before proceeding.[129] Additionally, patients with ICDs with terminal illnesses, such as advanced stage cancers, should have discussions regarding end-of-life care, with special consideration of timing of ICD de-activation.

Congestive Heart Failure

CHF is a common problem in the elderly, with 20% of hospital admissions of patients older than 65 years attributable to CHF each year.[130] Although CHF can be due to a variety of causes, the most common contributing factor in the elderly is CHD, followed by hypertension.[131] The morbidity of CHF in the elderly is related to decreased cardiac reserve, as discussed earlier, and the number of comorbid illnesses, such as atrial fibrillation and chronic kidney disease. CHF mortality is high, with up to one-third of elderly patients dying within 1 year of their initial CHF hospitalization.[132]

Systolic Heart Failure

Significant advances in treatment of CHF with systolic dysfunction have been made in the past 30 years, with many pharmacologic agents favorably altering the natural history of CHF. These medications are widely prescribed to elderly patients with CHF despite their underrepresentation in clinical trials.

Angiotensin-Converting Enzyme Inhibitors. The ACC/AHA guidelines recommend ACE-I for all patients with systolic CHF who do not have contraindications to their use.[133] Although most clinical trials did not exclude patients based on age, patients with low blood pressure and those with significant renal dysfunction were excluded. In a meta-analysis of 27 trials using ACE-I in patients with systolic CHF, patients older than 60 years had significant reductions in mortality or hospitalization (OR 0.79, 95% CI 0.66-0.95).[134] One trial that was significantly weighted toward the elderly was the Cooperative North Scandinavian Enalapril Survival Study (CONSENSUS), where the mean age was 71.[135] Patients with NYHA class IV systolic CHF treated with enalapril had a 31% relative risk reduction in mortality ($P = .001$) compared with conventional CHF therapy of the time, primarily digoxin and diuretics. A retrospective study of over 19 000 elderly nursing home residents found that patients treated with ACE-I had a 10% relative decrease in mortality compared to patients on digoxin alone.[136] Despite the paucity of evidence supporting their use, ACE-I are recommended in elderly patients with systolic heart failure. Although high doses of ACE-I are targets of therapy, initial doses in the elderly should be low and titration should be gradual, with frequent laboratory testing of serum potassium and creatinine, as well as evaluation for orthostatic hypotension.

Angiotensin II Receptor Blockers. Although less well-studied than ACE-I in CHF, ARB-II have the only large, randomized, clinical trials in the angiotensin-antagonist literature specifically targeted to the elderly: Evaluation of Losartan in the Elderly (ELITE) and ELITE II. The ELITE series of trials investigated patients over age 65 with symptomatic CHF with reduced LVEF who were randomized to either captopril or losartan.[137,138] The ELITE study showed a non-significant trend toward better survival in the losartan treated group; however, this was not seen in the larger ELITE II study. In both studies, losartan was better tolerated than captopril, mostly due to lower rates of cough. In subgroup analyses of the major trials of valsartan and candesartan, patients aged 65 and older had benefits of ARB-II use similar to younger patients.[139,140] In the Candesartan in Heart Failure Assessment of Reduction in Mortality and Morbidity (CHARM) overall program, analysis of the subgroup of patients 75 and older also showed significant benefit in cardiovascular death and hospitalization.[140] Finally, ARB-II are recommended as treatment for CHF in patients who are intolerant of ACE-I.[133]

Beta-Blockers. Three beta-blockers have been demonstrated in multiple large studies to be effective in reducing mortality in patients with chronic systolic CHF: bisoprolol, carvedilol, and sustained-release metoprolol succinate.[141–144] A meta-analysis of 5 studies using these 3 agents in over 12 000 patients showed a significant mortality benefit in patients 65 and older (relative risk 0.76, 95% CI 0.64-0.90) compared to younger patients.[145] For this reason, use of these agents is recommended in elderly patients with systolic CHF. A new beta-blocker, nebivolol, was studied in a randomized, controlled trial of 2128 patients age 70 and older, with CHF (regardless of LVEF) and not currently on

beta-blocker therapy.[146] In the Study of the Effects of Nebivolol Intervention on Outcomes and Rehospitalisation in Seniors with Heart Failure (SENIORS), at mean follow-up of 21 months, patients treated with nebivolol had a 4.2% absolute risk reduction in a composite of mortality or hospital admission ($P = .039$). Thus, it is reasonable to use nebivolol in the management of elderly patients with heart failure. Careful monitoring of heart rate is necessary when prescribing beta-blockers in the elderly.

Aldosterone Antagonists. Three large, randomized, placebo-controlled trials have demonstrated the efficacy of aldosterone antagonism, either by spironolactone or eplerenone, in patients with systolic CHF with mild to severe symptoms, as well as following myocardial infarction.[147–149] In the Randomized Aldactone Evaluation Study (RALES), 1663 patients with NYHA class III or IV systolic CHF already on ACE-I treatment were randomized to spironolactone 25 mg per day versus placebo.[147] Spironolactone was associated with a 30% relative risk reduction (11% absolute reduction, $P < .001$) in death. Subgroup analysis showed similar benefit in patients 65 and older. The Eplerenone Post-Acute Myocardial Infarction Heart Failure Efficacy and Survival Study (EPHESUS) subgroup analysis of patients 65 and older with a recent MI and a LVEF of 40% or less found no improvement in this older group, compared to marked improvement in mortality and hospitalizations seen in younger patients.[148] In contrast, patients 65 and older in the Eplerenone in Mild Patients Hospitalization and Survival Study in Heart Failure (EMPHASIS-HF) who had mild (NYHA II) CHF symptoms had significantly reduced rates of a composite end point of cardiac death or hospitalization.[149]

In all 3 trials, patients with significant renal dysfunction (serum creatinine of 2.5 or greater or estimated glomerular filtration rate of 30 ml/min or less) were excluded because of the risk of hyperkalemia. An observational study after the RALES trial demonstrated a nearly 4-fold increase in admissions for hyperkalemia with an associated mortality that increased 6-fold, temporally linked to a 4-fold increase in prescribing rates of spironolactone.[150] This demonstrates the importance of closely following serum potassium levels after initiation of aldosterone antagonists in elderly patients with subclinical renal disease. Patients with advanced renal failure or in whom close follow-up of serum potassium levels is not possible have an unfavorable risk-to-benefit ratio with aldosterone antagonists.

Vasodilator Therapy (Nitrates and Hydralazine). The benefits of vasodilator therapy in heart failure were demonstrated in the first large, randomized, clinical trial in chronic systolic heart failure management – the Veterans Administration Cooperative Vasodilator in Heart Failure Trial (V-HeFT), which randomized patients to prazosin, a combination of hydralazine and isosorbide dinitrate, or placebo.[151] Relative mortality at 2 years in the hydralazine-nitrate group was 34% lower than placebo ($P < .028$). There was no benefit in the prazosin-treated group compared to placebo. This study was conducted on patients whose only other CHF management was digoxin and diuretics; patients on beta-blockers, CCBs, or other nondiuretic antihypertensive drugs were excluded. The applicability of this trial to the elderly is limited, as the upper age limit in the trial was 75 and the mean age was 58; subgroup analysis did not show a difference in the mortality effect between patients older and younger than age 60.[152] A follow-up trial, V-HeFT II, evaluated enalapril (which had been shown in CONSENSUS to be efficacious in CHF) versus hydralazine-nitrate therapy.[153] Enalapril was superior to the combination of hydralazine and isosorbide dinitrate in reducing mortality at 2 years (18% in the enalapril arm versus 25% in the hydralazine-nitrate arm, $P = .016$). The V-HeFT investigators suggested that ACE-I and hydralazine-nitrates be used in combination in CHF patients, since both agents had shown benefit over placebo, but the trial investigating that combination was not performed for another decade. The African-American Heart Failure Trial (A-HeFT) investigators studied 1050 black patients with CHF who were already on standard CHF therapy (including 69% of patients on ACE-I and 17% on ARB-II).[154] They randomized these patients to the addition of either placebo or the combination of isosorbide dinitrate 40 mg 3 times a day and hydralazine 75 mg 3 times a day. The study was stopped prematurely after a mean follow-up of 10 months because of the significantly higher mortality rate in the placebo compared to the vasodilator arm (10.2% versus 6.2%, $P = .02$). In the V-HeFT II and A-HeFT trials, the populations were younger, with V-HeFT II excluding patients over age 75 and A-HeFT's mean age of 57.[153,154] Subgroup analysis of V-HeFT II showed no effect of age on mortality with ACE-I or vasodilator therapy; analysis of the A-HeFT trial showed a benefit in a weighted composite end point of mortality, hospitalization, and quality of life, but no mortality benefit in patients aged 65 and older.[155,156] In general, combination vasodilator therapy is recommended in patients with symptomatic heart failure who are already on maximal tolerated doses of other recommended CHF therapies, including beta-blockers and ACE-I.[133] Combination therapy with hydralazine and isosorbide dinitrate is a reasonable alternative to ACE-I or ARB-II in patients with recurrent renal failure or hyperkalemia on those medications, as is fairly common in elderly patients.

Digoxin. Cardiac glycosides were the first drugs used successfully for heart failure and, with diuretics, remained the mainstay of CHF therapy until the first large CHF trials were performed in the 1980s. The effectiveness of these agents was examined in a large randomized trial, performed by the Digoxin Investigation Group (DIG), which randomized 6800 patients with systolic CHF who were already on CHF therapy (including 94% on ACE-I and 82% on diuretics) to either digoxin or placebo.[157] There was no significant difference in mortality between the groups at 3 years follow-up; there were, however, significantly fewer hospitalizations in the digoxin group compared to placebo (26.8 versus 34.7%, $P < .001$). A post-hoc analysis of patients by age found no difference in mortality between patients aged 70 to 79 and those 80 and older, with a persistent benefit in fewer hospitalizations.[158] Digoxin continues to be recommended as a reasonable medication for the treatment of symptomatic CHF;[133] however, caution must be used in the elderly, especially elderly women, who have the highest risk of digoxin toxicity.[159]

Diuretics. Diuretic therapy is indicated for the management of symptoms of congestion and volume overload in CHF patients.[133] Diuretics have not been shown to reduce mortality in patients with CHF. A post-hoc analysis of the DIG study discussed above found that diuretic use was associated with an increase in risk of mortality and hospitalizations in patients age 65 and older.[160] Diuretics should be used judiciously in elderly patients, with frequent monitoring of serum electrolytes and renal function.

Cardiac Resynchronization Therapy. In patients with symptomatic heart failure and ventricular dyssynchrony, resynchronization

therapy with biventricular pacing proved effective in reducing mortality and improving quality of life in several large trials which included subgroup analyses of elderly patients.[161–163] The Multicenter InSync Randomized Clinical Evaluation (MIRACLE) study found that patients with NYHA III or IV CHF symptoms, a QRS duration >129 ms, and a LVEF of 35% or less had significant improvement in functional status and LVEF when the implanted cardiac resynchronization therapy (CRT) device was functioning, compared to the period when the device was inoperative.[161] A subsequent analysis of the MIRACLE study showed significant improvements in NYHA class ($P = .004$) and LVEF ($P = .008$) in patients over age 75 when the device was on compared to off.[164]

The Comparison of Medical Therapy, Pacing, and Defibrillation in Heart Failure (COMPANION) trial compared medical therapy to medical therapy plus CRT or medical therapy plus CRT and ICD.[162] There was a statistically significant absolute risk reduction in the primary endpoint of death or hospitalization of 12% with CRT alone or CRT/ICD ($P = .014$ and .010, respectively). Subgroup analysis of patients in COMPANION older than age 65 showed equal efficacy in the older group. The Cardiac Resynchronization-Heart Failure (CARE-HF) trial also showed significant benefit in death or major cardiac event hospitalizations in patients with CRT compared to medical therapy (39% versus 55%, $P < .0001$); subgroup analysis showed no heterogeneity between groups younger and older than 66.4 years.[163] Elderly patients with symptomatic systolic CHF with evidence of dyssynchrony and LVEF of 35% or less are candidates for CRT implantation.[133] The device usually implanted is a CRT/ICD combination. Discussion with elderly patients regarding the defibrillator is recommended, as some patients may wish to have the symptomatic benefit of the CRT device without the end-of-life issues raised by the ICD.[165]

Heart Failure With Normal Ejection Fraction/Diastolic Heart Failure

In the Cardiovascular Health Study (CHS), 67% of elderly women and 42% of elderly men with symptomatic CHF had a normal LVEF.[166] The most common risk factor for the development of heart failure with normal ejection fraction (HFNEF) in the elderly is systolic hypertension.[167] Despite the prevalence of this problem, no pharmaceutical trials have shown a mortality benefit. In a recent HFNEF trial, the CHARM-Preserved substudy of the previously mentioned CHARM trial, patients with CHF with an LVEF of >40% (27% of patients enrolled were 75 and older) were randomized to treatment with candesartan versus placebo for 36 months.[168] There was no effect of candesartan on death, but there was benefit in hospitalizations (15.2% versus 18.5%, $P = .017$). A trial investigating irbesartan found no difference in mortality or hospitalizations.[169] Since no beneficial clinical outcome data exist, treatment recommendations for HFNEF are based on expert opinion and observational literature. In general, the treatment of HFNEF involves control of hypertension and management of sodium/fluid status.[167]

CONCLUSIONS

Heart disease is extremely common in elderly patients and is their leading cause of death. As the number of elderly persons increases worldwide they will constitute the majority of patients with cardiovascular disease. Current guidelines for management of cardiovascular disease are based predominantly on trials which either included few elderly patients or excluded the elderly completely. Because of this, evidence for outcomes of recommended treatments for prevalent cardiac conditions in the elderly is lacking. The clinician must incorporate knowledge of the effects of aging on the cardiovascular system with the evidence that exists for making the best decisions in coordination with the health outcomes values of the individual aged patient.[170]

CONFLICTS OF INTEREST

None declared.

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