Epidemiology, Pathophysiology, Prognosis, and Treatment of Systolic and Diastolic Heart Failure

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Abstract: Underlying causes, risk factors, and precipitating causes of heart failure (HF) should be treated. Drugs known to precipitate or aggravate HF such as nonsteroidal antiinflammatory drugs should be stopped. Patients with HF and a low left ventricular ejection fraction (systolic heart failure) or normal ejection fraction (diastolic HF) should be treated with diuretics if fluid retention is present, with an angiotensin-converting enzyme (ACE) inhibitor or an angiotensin receptor blocker if the patient cannot tolerate an ACE inhibitor because of cough, angioneurotic edema, rash, or altered taste sensation, and with a beta blocker unless contraindicated. If severe systolic HF persists, an aldosterone antagonist should be added. If HF persists, isosorbide dinitrate plus hydralazine should be added. Calcium channel blockers should be avoided if systolic HF is present. Digoxin should be avoided in men and women with diastolic HF if sinus rhythm is present and in women with systolic HF. Digoxin should be given to men with systolic HF if symptoms persist, but the serum digoxin level should be maintained between 0.5 and 0.8 ng/mL.

Key Words: heart failure, beta blockers, angiotensin-converting enzyme inhibitors, diuretics, digoxin, aldosterone antagonists, isosorbide dinitrate, hydralazine

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Heart failure (HF) affects approximately 5 million persons in the United States and more than 500,000 new cases of HF are reported each year.[1] Approximately 300,000 persons die of HF each year.[1] HF is predominantly a disease of the elderly with prevalence rates ranging from 1% in persons younger than 50 years to 10% in persons aged 80 years and older.[2] Approximately 80% of patients hospitalized with HF are older than 65 years.[1] HF is not only the most common cause of hospitalization in the United States, but is also the most costly with annual expenditures of more than $40 billion spent each year.[3] At 46-month follow up of 1160 men, mean age 80 years, and of 2464 women, mean age 81 years, HF developed in 29% of men and in 26% of women.[4]

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EPIDEMIOLOGY

Coronary artery disease (CAD) and hypertension are the 2 major risk factors for the development of HF in older persons. Other common etiologies include diabetes mellitus, valvular heart disease, especially aortic stenosis and mitral regurgitation, and nonischemic cardiomyopathies. Frequently, HF in older persons is multifactorial.

Older patients with hypertension and echocardiographic left ventricular (LV) hypertrophy had a 2.6 times higher incidence of HF than those with hypertension and no left ventricular (LV) hypertrophy.[5] Electrocardiographic (ECG) LV hypertrophy and diabetes mellitus are also risk factors for the development of HF in older persons.[5–7] At 43-month follow up of 2902 patients (926 men and 1976 women), mean age 81 years, HF developed in 27% of patients.[8] Significant independent risk factors for the development of HF were male gender (risk ratio = 1.4), hypertension (risk ratio = 2.5), CAD (risk ratio = 4.0), diabetes mellitus (risk ratio = 1.6), and age (risk ratio = 1.05 for each 1-year increase in age).[8]

Table 1 lists common precipitating factors of HF in elderly patients. Nonsteroidal antiinflammatory drugs (NSAIDs) should be avoided because these drugs precipitate HF; aggravate HF; contribute to renal insufficiency in patients with HF; cause sodium and fluid retention, vasoconstriction, and hypertension; interfere with the efficacy of antihypertensive drugs such as diuretics, angiotensin-converting enzyme (ACE) inhibitors, beta blockers, and vasodilators; and interfere with the efficacy of diuretics in patients with HF. These adverse effects of NSAIDs apply to cyclooxygenase-2-specific inhibitors as well as cyclooxygenase-1 inhibitors. Calcium channel blockers should be avoided because they worsen HF by activating neurohormonal systems. Disopyramide and other antiarrhythmic drugs except for beta blockers, digoxin, and amiodarone should be avoided because their negative inotropic effects worsen HF.

PATHOPHYSIOLOGY

There is a progressive loss of myocytes and hypertrophy of the remaining myocytes with aging.[9] The maximal heart rate, maximal cardiac output, and maximal VO_2 progressively decrease with aging.[9] The maximal stroke

TABLE 1. Common Precipitating Factors of Heart Failure

Dietary sodium excess
Excess fluid intake
Inadequate treatment
Nonadherence to appropriate drugs
Uncontrolled hypertension
Use of inappropriate drugs such as nonsteroidal antiinflammatory drugs
Anemia
Infection
Fever
Hypoxia
Hot, humid environment
Alcohol
Bradyarrhythmias
Tachyarrhythmias
Myocardial infarction or ischemia
Pulmonary embolism
Renal insufficiency
Hyperthyroidism
Hypothyroidism

volume may be maintained or decreased with aging.[9] Systemic vascular resistance is increased with aging.[9]

With aging, LV stiffness is increased, LV compliance is decreased, systolic blood pressure is increased, LV wall thickness is increased, early LV diastolic filling is decreased with a greater contribution to LV filling resulting from left atrial systole, and LV relaxation is impaired.[9,10] With aging, there is deconditioning of the skeletal muscles and a decreased vasodilator response to exercise.[9] With aging, there is also a progressive reduction in the ability to excrete sodium.[9]

Aging is associated with a prolongation of isovolumic relaxation time and with a slowing of the rate at which calcium is sequestered by the sarcoplasmic reticulum after myocardial relaxation, which results in reduced relaxation of the LV.[10–13] Accumulation of calcium at the onset of diastole may decrease LV diastolic relaxation and early LV diastolic filling.[12] Reduced oxidative phosphorylation and cumulative mitochondrial peroxidation occur with aging and may also reduce LV diastolic function.[14,15]

Increased LV stiffness occurs with aging because of increased interstitial fibrosis and crosslinking of collagen in the heart. Increased LV stiffness decreases LV diastolic relaxation and filling.[16–19] A decrease in capillary density and coronary reserve in the absence of CAD occurs with aging, causes myocardial ischemia, and may further reduce LV diastolic function in elderly persons.[16,20]

Older persons are also more likely to have decreased LV diastolic function because they have a higher prevalence of hypertension, myocardial ischemia caused by CAD, and LV hypertrophy caused by hypertension, aortic stenosis, CAD, hypertrophic cardiomyopathy, and other cardiac disorders.[21] The increased stiffness of the LV and prolonged LV relaxation time decrease LV early diastolic filling and cause higher LV end-diastolic pressures at rest and during exercise in elderly persons.[22,23]

In HF, the heart is unable to deliver an adequate cardiac output to supply the tissue needs despite an adequate LV filling pressure. LV systolic dysfunction, LV systolic plus diastolic dysfunction, or LV diastolic dysfunction with normal LV systolic function (diastolic HF) may be present in HF.

Remodeling stimuli such as increased mechanical LV wall stress, neurohormonal activation, cytokines, and oxidative stress lead to hypertrophy of cardiac myocytes, alterations in the interstitial matrix, fetal gene expression, and myocyte death. These events lead to changes in the structure and function of the LV, which results in further LV dysfunction and increased LV wall stress, promoting more pathologic remodeling. Myocyte loss may occur either by necrosis or apoptosis.

Reduced myocardial contractility may cause HF with low LV ejection fraction. Increased myofibril stress is needed to maintain stroke volume. Increased sarcomere length resulting from increased LV diastolic volume is needed because of increased LV wall stress. Myocellular hypertrophy and increased myocardial mass result from increased LV wall stress, loss of myocytes, and decreased myocardial contractility. LV chamber enlargement develops because of lengthening of myocytes from sarcomere growth in series or from cell slippage.

Constriction of the peripheral circulation occurs. The increased afterload is associated with a further increase in preload and muscle mass but with a decreased velocity and extent of myocardial fiber shortening. Cardiac output and stroke volume become reduced initially during exercise and later at rest.

In HF associated with LV systolic dysfunction, LV ejection fraction is reduced ($<$50%). There is a decreased amount of myocardial fiber shortening, the stroke volume is decreased, the LV is dilated, and the patient is symptomatic.

The LV ejection fraction is normal ($\geq$50%) in patients with diastolic HF. During exercise, persons with normal LV systolic function but abnormal LV diastolic function are unable to normally increase stroke volume even in the presence of increased LV filling pressure.[24] Myocardial hypertrophy, ischemia, or fibrosis causes slow or incomplete LV filling at normal left atrial pressures. Left atrial pressure rises to increase LV filling, resulting in pulmonary and systemic venous congestion.

The incidence of chronic atrial fibrillation increases with age.[25–27] The prevalence of chronic atrial fibrillation was 16% in 1160 men, mean age 80 years, and 13% in 2464 women, mean age 81 years.[4] The development of atrial fibrillation may cause a reduction in cardiac output and the development of pulmonary and systemic venous congestion because of the loss of left atrial contribution to LV late diastolic filling and a shortened diastolic filling time caused by a rapid ventricular rate.

The prevalence of diastolic heart failure increases with age[8,28–34] and is higher in older women than in older men.[8,29–34] In the New York Heart Failure Consortium Registry on Diastolic Dysfunction, the patients were predominantly elderly women with longstanding hypertension and

TABLE 2. Prevalence of Diastolic Heart Failure in the Elderly With Heart Failure

Study	Normal Left Ventricular Ejection Fraction
Wong WF, et al[28]	41% of 54 patients, mean age 80 yr
Aronow WS, et al[29]	47% of 247 patients, mean age 82 yr
Pernenkil R, et al[30]	34% of 501 patients aged ≥70 yr
Aronow WS, et al[31]	50% of 572 patients, mean age 82 yr
Aronow WS, et al[8]	51% of 674 patients, mean age 81 yr
Framingham Study[32]	51% of 73 patients, mean age 73 yr
Cardiovascular Health Study[33]	63% of 269 patients, mean age 74 yr

increased left ventricular mass.[34,35] Table 2 shows the prevalence of diastolic HF in older persons with HF.[8,28–33]

Table 3 shows the association of diastolic HF with gender for different age groups.[31] Diastolic HF was present in 44% of 55 older black men versus 58% of 110 older black women with HF, in 46% of 24 older Hispanic men versus 56% of 34 older Hispanic women with HF, and in 35% of 148 older white men versus 57% of 303 older white women with HF.[8]

Chronic stimulation of the sympathetic nervous system with increased plasma levels of norepinephrine occurs during HF and is increased with aging. Chronic stimulation of the sympathetic nervous system causes sympathetic-mediated peripheral vasoconstriction and renal retention of sodium and water. Plasma norepinephrine levels correlate directly with prognosis in patients with chronic HF.[36] Figure 1 shows adverse effects of neurohormal activation in patients with chronic HF.

Increased sympathetic activity leads to increased levels of plasma arginine vasopressin, atrial natriuretic peptide, and brain natriuretic peptide levels in patients with chronic HF. Increased sympathetic activity also activates the renin–angiotensin–aldosterone system in patients with HF. Increased angiotensin II levels result from increased renal renin secretion by several mechanisms. Plasma renin levels are often elevated in patients with HF but the increase is variable. Plasma renin levels in patients with HF are inversely related to the serum sodium concentration.

The major neurohormonal systems activated in HF are the sympathetic nervous system, the renin–angiotensin–aldosterone system, natriuretic peptides, endothelin, and tumor necrosis factor alpha. Reflex activation of the neurohormonal systems with chronic HF is no longer a compensatory mechanism to maintain arterial pressure and cardiac output but

TABLE 3. Association of Diastolic Heart Failure With Age and Gender in Elderly Patients With Heart Failure

Age (years)	Diastolic Heart Failure
60–69	22% of 18 men and 37% of 38 women
70–79	33% of 54 men and 44% of 79 women
80–89	41% of 86 men and 59% of 219 women
≥90	47% of 19 men and 73% of 59 women

Adapted from Aronow WS, Ahn C, Kronzon I. Normal left ventricular ejection fraction in older persons with congestive heart failure. *Chest.* 1998;113:867–869.

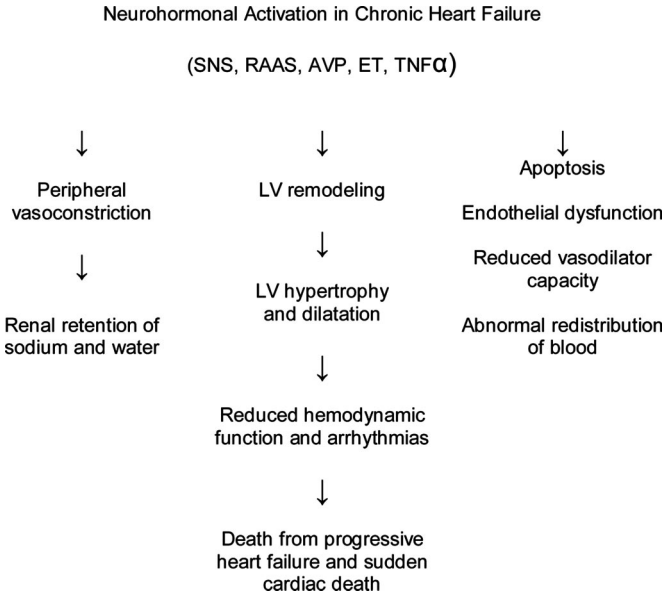

FIGURE 1. Effects of neurohormal activation in chronic heart failure. SNS indicates sympathetic nervous system; RAAS, renin–angiotensin–aldosterone system; AVP, arginine vasopressin; ET, endothelin-A receptors; TNFα, tumor necrosis factor α receptors; LV, left ventricular.

adversely affects outcome by leading to apoptosis, endothelial dysfunction, reduced vasodilator capacity, abnormal redistribution of blood, and other problems that are harmful to the patient. Stimulation of inflammatory cytokines increases oxidative stress.

Activation of the neurohormonal systems leads to LV remodeling and LV systolic dysfunction. The LV becomes more spherical and dilated. LV remodeling causes increased LV wall tension, increased myocardial oxygen consumption, reduced subendocardial perfusion, and reduced myocyte shortening. LV remodeling affects prognosis by reducing hemodynamic function and by increasing the risk of arrhythmias leading to sudden cardiac death. Activation of neurohormonal systems in chronic HF increases LV hypertrophy and later LV dilatation by alterations in afterload, preload, stretch, increased wall stress, interstitial collagen deposits, and direct toxic effects.

STAGES OF HEART FAILURE

The American College of Cardiology (ACC)/American Heart Association (AHA) guidelines for the evaluation and management of HF state that there are 4 stages of HF.[1] Patients with stage A HF are at high risk of developing HF because of the presence of conditions strongly associated with the development of HF.[1] These patients have hypertension, CAD, diabetes mellitus, a history of cardiotoxic drug therapy, alcohol abuse, a history of rheumatic fever, or a family history of cardiomyopathy. These patients have no evidence of structural heart disease.

Patients with stage B HF have structural heart disease associated with the development of HF but have never shown symptoms or signs of HF.[1] These patients have a prior

myocardial infarction (MI), LV hypertrophy or fibrosis, LV dilatation or hypocontractility, or asymptomatic valvular heart disease.[1]

Patients with stage C HF have current or prior symptoms of HF associated with structural heart disease.[1] Patients with stage D HF have advanced structural heart disease and marked symptoms of HF at rest despite maximal medical therapy and who require specialized interventions.[1]

PROGNOSIS OF HEART FAILURE

Table 4 shows the mortality rates in the different studies of older patients with HF and normal versus abnormal LV ejection fraction.[29,30,32,33,37] Table 5 shows the 1-year, 2-year, 3-year, 4-year, and 5-year mortality rates in men and in women with HF after prior MI and normal versus low LV ejection fraction.[37] In this study, the Cox regression model showed that abnormal LV ejection fraction was a significant independent risk factor for mortality with a risk ratio of 2.2.[37] This study also found that the mortality rates were similar in men versus women with normal or low LV ejection fraction.[37]

In another study of 132 patients, mean age 82 years, with atrial fibrillation, prior MI, and HF and of 223 patients, mean age 79 years, with sinus rhythm, prior MI, and HF, the mortality rates were significantly higher in patients with atrial fibrillation and low or normal LV ejection fraction.[38] In this study, the Cox regression model showed that atrial fibrillation and abnormal LV ejection fraction were significant independent risk factors for mortality with risk ratios of 1.5 and 2.2, respectively.[38]

TABLE 4. Mortality Rates in Older Patients With Heart Failure

Study	Mortality Rates
Aronow WS, et al[29]	In patients with CAD, the 1-yr mortality rate was 22% in 68 patients with normal LVEF and 47% in 98 patients with low LVEF; the 4-yr mortality rate was 56% in patients with normal LVEF and 85% in patients with low LVEF
Pernenkil R, et al[30]	The 1-yr mortality rate was 28% in 171 patients with normal LVEF and 38% in 228 patients with low LVEF
Framingham Study[32]	At 6.2-yr median follow up, the annual mortality rate was 19% in patients with abnormal LVEF, 9% in 37 patients with normal LVEF, and 3% in 74 control patients
Aronow WS, et al[37]	In patients with prior myocardial infarction, the 1-yr mortality rate was 19% in 226 patients with normal LVEF and 41% in 340 patients with low LVEF; the 5-yr mortality rate was 74% in patients with normal LVEF and 92% in patients with low LVEF
Cardiovascular Health Study[33]	The mortality rate was 87 deaths per 1000 person-years in 170 patients with normal LVEF, 115 deaths per 1000 person-years in 39 patients with borderline LVEF (45–54%), and 154 deaths per 1000 person-years in 60 patients with low LVEF (<45%)

LVEF indicates left ventricular ejection fraction; CAD, coronary artery disease.

TABLE 5. Mortality Rates in Men and in Women With Heart Failure After Prior Myocardial Infarction

Mortality at	Men With Normal LVEF (n = 65)	Men With Low LVEF (n = 133)	Women With Normal LVEF (n = 211)	Women With Low LVEF (n = 207)
1 yr	20%	41%	19%	41%
2 yr	38%	63%	39%	66%
3 yr	51%	78%	48%	78%
4 yr	57%	85%	56%	86%
5 yr	75%	92%	74%	92%

Adapted from Aronow WS, Ahn C, Kronzon I. Prognosis of congestive heart failure after prior myocardial infarction in older men and women with abnormal versus normal left ventricular ejection fraction. *Am J Cardiol.* 2002;85:1382–1384.

LVEF indicates left ventricular ejection fraction.

The treatment of choice for HF associated with severe valvular aortic stenosis or with severe valvular aortic regurgitation is surgical replacement of the aortic valve.[39] At 19-month follow up, 90% of 30 elderly patients with HF and unoperated severe valvular aortic stenosis and normal LV ejection fraction were dead.[40] At 13-month follow up, 100% of 18 elderly patients with HF and unoperated severe valvular aortic stenosis and low LV ejection fraction were dead.[40]

At 24-month follow up, 88% of 17 elderly patients with HF and unoperated severe valvular aortic regurgitation and normal LV ejection fraction were dead.[41] At 15-month follow up, 100% of 8 elderly patients with HF and unoperated severe aortic valvular regurgitation and low LV ejection fraction were dead.[41]

TREATMENT OF STAGE A HEART FAILURE

In patients with stage A HF, treat hypertension,[1,42,43] treat lipid disorders,[1,44–52] encourage regular exercise, avoid smoking, alcohol consumption, and illicit drug use, control the ventricular rate in patients with supraventricular tachyarrhythmias, and use ACE inhibitors in patients with atherosclerotic vascular disease, diabetes mellitus, or hypertension.[1] Patients with diabetes should be treated as if they had CAD.[53] Educational programs may have to be used to increase the use of lipid-lowering drugs.[54,55]

TREATMENT OF STAGE B HEART FAILURE

The ACC/AHA guidelines recommend, in patients with stage B HF treatment with all stage A measures, treatment with ACE inhibitors and beta blockers, and valve replacement or repair for patients with hemodynamically significant valvular stenosis or regurgitation.[1]

GENERAL MEASURES FOR TREATMENT OF STAGE C HEART FAILURE

Underlying causes of HF should be treated when possible. Precipitating causes of HF (Table 1) should be identified and treated. Hypertension should be treated with diuretics, ACE inhibitors, and beta blockers. Myocardial ischemia should be treated with nitrates and beta blockers.

Older persons with HF without contraindications to coronary revascularization who have exercise-limiting angina

pectoris, angina pectoris occurring frequently at rest, or recurrent episodes of acute pulmonary edema despite optimal medical therapy should have coronary angiography. Coronary artery bypass graft surgery or percutaneous transluminal coronary angioplasty should be performed in selected patients with myocardial ischemia attributable to viable myocardium subserved by severely stenotic coronary arteries.

Selected patients should have surgical correction of valvular lesions, surgical excision of a dyskinetic LV aneurysm, surgical correction of a systemic arteriovenous fistula, and surgical resection of the pericardium for constrictive pericarditis if clinically indicated. Infective endocarditis should be treated with intravenous antibiotics and with surgical replacement of valvular lesions if clinically indicated. Anemia, infection, bronchospasm, hypoxia, tachyarrhythmias, bradyarrhythmias, obesity, hyperthyroidism, and hypothyroidism should be treated.

Oral warfarin should be administered to patients with HF who have prior systemic or pulmonary embolism, atrial fibrillation, or cardiac thrombi detected by 2-dimensional echocardiography. The dose of warfarin administered should achieve an international normalized ratio of 2.0 to 3.0. A surgical procedure should be performed if anticoagulant therapy fails to prevent pulmonary embolism. Beriberi heart disease should be treated with thiamine. A transvenous pacemaker should be implanted into the right ventricle of a patient with HF who has complete atrioventricular block or severe bradycardia.

Patients with HF should have their sodium intake decreased to 1.6 to 2.0 g of sodium (4–5 g of sodium chloride) daily. Spices and herbs instead of sodium chloride should be used to flavor food. Normal fluid intake with sodium restriction is the general recommendation. Fluid intake should be restricted if dilutional hyponatremia develops and the serum sodium concentration falls below 130 mEq/L. Patient compliance should be stressed such as the need for salt restriction, fluid restriction, and daily weights through patient education.

Patients with HF should avoid exposure to heavy air pollution. Air conditioning is essential for patients with HF who are in a hot, humid environment. Ethyl alcohol intake should be avoided. Medications such as NSAIDs and antiarrhythmic drugs other than beta blockers, digoxin, and amiodarone, which precipitate or exacerbate HF, should be stopped. Regular physical activity such as walking should be encouraged in patients with mild to moderate HF to improve functional status and to decrease symptoms. Patients with HF who are dyspneic at rest at a low work level may benefit from a formal cardiac rehabilitation program.[56] A multidisciplinary approach to care is useful.[57]

Diuretics

Diuretics are the first-line drug in the treatment of older patients with HF and volume overload. Diuretics decrease venous return, reduce ventricular filling pressures, cause loss of fluid from the body, and decrease symptoms of pulmonary and systemic congestion and edema. Age-related decreases in renal function and in circulating plasma volume may decrease the efficacy of diuretics in elderly patients with HF.

A thiazide diuretic such as hydrochlorothiazide may be used to treat older patients with mild HF. However, a thiazide diuretic is ineffective if the glomerular filtration rate is less than 30 mL/min. Older patients with moderate or severe HF should be treated with a loop diuretic such as furosemide. NSAIDs should not be taken by these patients because these drugs may inhibit the induction of diuresis by furosemide. Older patients with severe HF or concomitant renal insufficiency may need the addition of metolazone to the loop diuretic. Severe volume overload should be treated with intravenous diuretics and hospitalization.

Older patients with HF treated with diuretics need close monitoring of their serum electrolytes. Hypokalemia and hypomagnesemia, both of which may precipitate ventricular arrhythmias and digitalis toxicity, may develop. Hyponatremia with activation of the renin–angiotensin–aldosterone system may occur.

Elderly patients with HF are especially sensitive to volume depletion. Dehydration and prerenal azotemia may occur if excessive doses of diuretics are given. Therefore, the minimum effective dose of diuretics should be used. Older patients with HF and volume overload associated with low or normal LV ejection fraction should be treated with diuretics (Tables 6 and 7). However, elderly patients with HF and low LV ejection fraction tolerate higher doses of diuretics than do elderly patients with HF and normal LV ejection fraction. Elderly patients with diastolic heart failure require high LV filling pressures to maintain an adequate stroke volume and cardiac output and cannot tolerate intravascular depletion. Therefore, elderly patients with HF and normal LV ejection fraction should be treated with a low sodium diet with cautious use rather than with large doses of diuretics. The

TABLE 6. American College of Cardiology/American Heart Association 2001 Guidelines for Treatment of Heart Failure With Low Left Ventricular Ejection Fraction

Class I Recommendations

1. Therapeutic measures for stages A and B heart failure
2. Diuretics in patients with fluid retention
3. Angiotensin-converting enzyme inhibitors unless contraindicated
4. Beta blockers unless contraindicated
5. Digoxin for the treatment of persistent symptoms of heart failure
6. Withdrawal of drugs known to precipitate or aggravate heart failure such as nonsteroidal antiinflammatory drugs, calcium channel blockers, and most antiarrhythmic drugs

Class II_a Recommendations

1. Aldosterone antagonist in patients with class IV symptoms, preserved renal function, and normal serum potassium
2. Exercise training as an adjunctive approach to improve clinical status in ambulatory patients
3. Angiotensin receptor blockers in patients who cannot be given an angiotensin-converting enzyme inhibitor because of cough or angioedema
4. Hydralazine plus nitrates in patients being treated with diuretics, beta blockers, and digoxin who cannot be given an angiotensin-converting enzyme inhibitor because of hypotension or renal insufficiency

Adapted from *J Am Coll Cardiol.* 2001;38:2101–2113.

TABLE 7. Treatment of Older Patients With Diastolic Heart Failure

1. Treat with cautious use of diuretics and with beta blockers
2. Add angiotensin-converting enzyme (ACE) inhibitors if heart failure persists or angiotensin II type 1 receptor antagonists if patient cannot tolerate ACE inhibitors because of cough, angioneurotic edema, rash, or altered taste sensation
3. Add isosorbide dinitrate plus hydralazine if heart failure persists
4. Add calcium channel blocker if heart failure persists
5. Avoid digoxin if sinus rhythm is present

dose of diuretics should be gradually reduced and stopped if possible when fluid retention is not present in patients with HF and low or normal LV ejection fraction. Patients on high doses of diuretics had increased mortality.[58]

Angiotensin-Converting Inhibitors

ACE inhibitors are balanced vasodilators that decrease both afterload and preload. ACE inhibitors reduce systemic vascular resistance, arterial pressure, LV and right ventricular end-diastolic pressures, cardiac work, and myocardial oxygen consumption and increase cardiac output. ACE inhibitors decrease circulating levels of angiotensin II, reduce sympathetic nervous system activity, stimulate prostaglandin synthesis, and decrease sodium and water retention by inhibiting angiotensin II stimulation of aldosterone release. ACE inhibitors are very effective in treating HF associated with low LV ejection fraction (Table 6). The ability of ACE inhibitors to block aldosterone production is only partial and limited to approximately the first 6 months of therapy with loss of efficacy afterward.

ACE inhibitors may also improve HF associated with normal LV ejection fraction by decreasing afterload, lowering elevated blood pressure, decreasing LV mass and arterial and arteriolar wall thickness and stiffness by improving LV relaxation and by attenuating the coronary vasoconstriction of angiotensin II. Increased activation of the renin–angiotensin–aldosterone system may stimulate the progression of myocardial fibrosis.[59] ACE inhibitors may also improve LV diastolic function by causing regression of myocardial interstitial fibrosis.

ACE inhibitors improve symptoms, quality of life, and exercise tolerance in patients with HF. ACE inhibitors also increase survival in patients with HF and low LV ejection fraction (Table 8)[60–64] and should be used to treat patients with HF and low LV ejection fraction (Table 6).[1] ACE inhibitors also improve survival and reduce the incidence of HF and coronary events in patients with low LV ejection fraction without HF (Table 9)[65–68] and should be used to treat these patients.[1]

At 3-month follow up of older persons with prior MI and diastolic HF treated with diuretics, patients randomized to enalapril had significant improvements in New York Heart Association (NYHA) functional class, in treadmill exercise time, in LV ejection fraction, and in LV diastolic function assessed by Doppler echocardiography.[69] Enalapril also significantly decreased cardiothoracic ratio measured from chest x-rays and echocardiographic LV mass.[69]

In an observational study of patients (55% women), mean age 75 years, with HF, 147 of 227 patients (65%) with a LV ejection fraction of 40% to 49% and 137 of 312 patients (44%) with a LV ejection fraction of ≥50% were treated with ACE inhibitors.[70] At 6-month follow up, ACE inhibitors significantly decreased mortality 63% ($P = 0.01$) and significantly improved quality-of-life scores ($P = 0.02$) in patients with a LV ejection fraction of 40% to 49% and insignificantly decreased mortality 39% and significantly improved quality-of-life scores ($P = 0.04$) in patients with a LV ejection fraction ≥50%.[70]

On the basis of these limited data,[70,71] persons with diastolic HF should be treated with ACE inhibitors (Table 7). However, data from large-scale, prospective, randomized, placebo-controlled studies investigating the efficacy of ACE inhibitors on cardiovascular mortality and morbidity are needed to establish the role of ACE inhibitors in the treatment of diastolic HF.

ACE inhibitors should be started in older persons with HF in low doses after correction of hyponatremia or volume depletion. It is important to avoid overdiuresis before initiat-

TABLE 8. Effect of Angiotensin-Converting Enzyme Inhibitors on Survival in Patients With Heart Failure and Low Left Ventricular Ejection Fraction

Study	Results
Cooperative North Scandinavian Enalapril Survival Study[60]	Compared with placebo, enalapril significantly decreased mortality 40% at 6 mo, 31% at 1 yr, and 27% at end of study
Veterans Administration Cooperative Vasodilator-Heart Failure Trial II[61]	Compared with hydralazine plus isosorbide dinitrate, enalapril significantly decreased mortality 28% at 2 yr
Studies of Left Ventricular Dysfunction Treatment Trial[62]	At 41-mo follow up, compared with placebo, enalapril significantly decreased mortality by 16%, death resulting from progressive heart failure by 22%, and mortality or hospitalization for worsening heart failure by 26%
Acute Infarction Ramipril Efficacy Study[63]	At 15-mo follow up of patients with myocardial infarction and heart failure, compared with placebo, ramipril significantly decreased mortality by 27% (36% in patients aged ≥65 yr)
Overview of 32 randomized trials of ACE inhibitors on mortality and morbidity in patients with heart failure[64]	Compared with placebo, ACE inhibitors significantly reduced mortality by 23% and mortality or hospitalization for heart failure by 35%

ACE indicates angiotensin-converting enzyme.

TABLE 9. Effect of Angiotensin-Converting Enzyme Inhibitors on Survival and Incidence of Heart Failure in Persons With Asymptomatic Low Left Ventricular Ejection Fraction

Study	Results
Survival and Ventricular Enlargement Trial[65]	At 42-mo follow up, compared with placebo, captopril significantly decreased mortality 19% (25% in patients aged ≥65 yr), death from cardiovascular causes 21%, development of severe heart failure 37%, development of heart failure requiring hospitalization 22%, and recurrent myocardial infarction 25%
Studies of Left Ventricular Dysfunction Prevention Trial[66]	At 37-mo follow up, compared with placebo, enalapril significantly decreased death plus heart failure 29% and death plus hospitalization for heart failure 20%
Trandolapril Cardiac Evaluation Study[67]	At 24- to 50-mo follow up, compared with placebo, trandolapril significantly decreased mortality 22% and progression to severe heart failure 29%
Aronow WS, et al [68]	At 34-mo follow up, ACE inhibitor therapy alone significantly decreased new coronary events 17% and heart failure 32%

ACE indicates angiotensin-converting enzyme.

ing treatment with ACE inhibitors because volume depletion may cause hypotension or renal insufficiency when ACE inhibitors are started or when the dose of these drugs is increased to full therapeutic levels. After the maintenance dose of ACE inhibitors is reached, it may be necessary to increase the dose of diuretics. Table 10 lists the initial dose and maintenance dose of ACE inhibitors used for treating HF in older persons.

Patients with HF and abnormal LV ejection fraction were randomized to 2.5 to 5.0 mg lisinopril daily versus 32.5 to 35 mg daily.[71] At 39-month to 58-month follow up, compared with low-dose lisinopril, high-dose lisinopril caused an 8% insignficant reduction in mortality, a significant 12% reduction in mortality or all-cause hospitalization, and a significant 24% reduction in hospitalization for HF.[71] The discontinuation of the study drug was similar for the 2 treatment groups. These data indicate that patients with HF should be treated with high doses of ACE inhibitors unless low doses are the only doses that can be tolerated.

In the Veterans Administration Cooperative Vasodilator–Heart Failure Trial II, compared with isosorbide dinitrate plus hydralazine, enalapril significantly reduced 2-year mortality by 28% because of a greater response to enalapril in whites than in blacks.[61] This led to the study of isosorbide dinitrate versus placebo in blacks with HF.[72] A report from the Studies of Left Ventricular Dysfunction databases showed that whites but not blacks randomized to enalapril had a significant reduction in the risk of hospitalization for HF.[73] However, a post hoc analysis of the 4054 black and white participants in the Studies of Left Ventricular Dysfunction Prevention Trial was performed to investigate whether enalapril had similar efficacy in preventing symptomatic HF in blacks versus whites.[74] Despite the increased absolute risk in blacks compared with whites for the progression of asymptomatic LV dysfunction, enalapril was equally efficacious in decreasing the risk of HF in blacks versus whites.[74]

TABLE 10. Initial Dose and Maintenance Dose of Angiotensin-Converting Enzyme Inhibitors for Therapy of Heart Failure in Older Persons

Drug	Initial Dose	Maintenance Dose
Benazepril	5 mg	5–40 mg daily
Captopril	6.25 mg 3 times per day	6.25–150 mg 3 times per day
Enalapril	2.5 mg	2.5 mg daily to 20 mg twice a day
Fosinopril	10 mg	10–40 mg daily
Lisinopril	2.5 mg	2.5–40 mg daily
Perindopril	4 mg	4–8 mg daily
Quinapril	5 mg	5 mg daily to 20 mg twice a day
Ramipril	2.5 mg	2.5 mg daily to 10 mg twice a day

Older patients at risk for excessive hypotension should have their blood pressure monitored closely for the first 2 weeks of ACE inhibitor therapy and whenever the physician increases the dose of ACE inhibitor or diuretic. Renal function should be monitored in patients administered ACE inhibitors to detect increases in blood urea nitrogen and in serum creatinine, especially in older patients with renal artery stenosis. A doubling in serum creatinine should cause the physician to consider renal dysfunction caused by ACE inhibitors, a need to reduce the dose of diuretics, or exacerbation of HF. Potassium supplements and potassium-sparing diuretics should not be given to patients receiving ACE inhibitors because ACE inhibitor therapy may cause hyperkalemia by blocking aldosterone production.

Asymptomatic hypotension with a systolic blood pressure between 80 and 90 mm Hg and a serum creatinine of less than 2.5 mg/dL are side effects of ACE inhibitors that should not necessarily cause discontinuation of this drug but should cause the physician to reduce the dose of diuretics if the jugular venous pressure is normal and to consider decreasing the dose of ACE inhibitor. Contraindications to the use of ACE inhibitors are symptomatic hypotension, progressive azotemia, angioneurotic edema, hyperkalemia, intolerable cough, and rash.

ACE inhibitors inhibit the metabolic degradation of bradykinin, which promotes vascular synthesis of vasodilating prostaglandins.[75] Aspirin is a cyclooxygenase inhibitor, which dose-dependently inhibits synthesis of prostaglandins in vascular tissues.[76] Aspirin in doses of less than 100 mg daily provides the desired antiplatelet effect without inhibiting synthesis of prostaglandins.

There are conflicting data about the importance of the negative interaction of aspirin with ACE inhibitors in the

treatment of patients with HF. Some hemodynamic studies support the importance of this negative interaction,[77,78] whereas other hemodynamic studies do not.[79,80] Retrospective analyses of clinical studies have also found conflicting data with some studies supporting[81,82] and other studies not supporting[83–85] a negative interaction between aspirin and ACE inhibitors. In a study of older patients with HF treated with ACE inhibitors, aspirin significantly reduced mortality by 31%.[85]

Until data from controlled clinical trials are available, a prudent approach to this controversy might be to reduce the dose of aspirin to 80 to 100 mg daily or substitute clopidogrel as an antiplatelet drug in patients with HF treated with ACE inhibitors. The dose of ACE inhibitors could also be increased to overcome aspirin-related attenuation.

Angiotensin Receptor Blockers

Angiotensin II is a potent vasoconstrictor that may cause impairment of LV function and progression of HF through increased impedance of LV emptying, adverse long-term structural effects on the heart and vasculature,[86] and activation of other neurohormonal agonists, including norepinephrine, aldosterone, and endothelin.[87]

The angiotensin II type 1 receptor antagonist losartan significantly reduced the rate of first hospitalization for HF 32% compared with placebo at 3.4-year follow up of patients with type 2 diabetes mellitus and nephropathy.[88] Losartan also significantly decreased hospitalization for HF 41% compared with atenolol at 4.7-year follow up of patients with diabetes with hypertension and electrocardiographic LV hypertrophy.[89]

In the Losartan Heart Failure Survival Study (ELITE) II, 3152 patients aged ≥60 years with NYHA class II–IV HF and a LV ejection fraction of ≤40% were randomized in a double-blind trial to receive 50 mg losartan daily or 50 mg captopril 3 times daily.[90] Median follow up was 555 days. Significantly more patients discontinued captopril because of adverse effects (14.7%) than losartan (9.7%).[90]

Mortality was 13% insignificantly lower in patients treated with captopril than in patients treated with losartan, 77% significantly lower in patients treated with captopril plus beta blockers than in patients treated with losartan plus beta blockers, and 5% insignificantly lower in patients treated with captopril without beta blockers than in patients treated with losartan without beta blockers.[90] Hospital admissions for any cause were 4% insignificantly higher in patients treated with losartan than in patients treated with captopril.[90] The ACC/AHA guidelines recommend using angiotensin receptor blockers in patients with HF who cannot be treated with an ACE inhibitor because of cough or angioneurotic edema with a class IIa recommendation (Table 6).[1]

The Valsartan Heart Failure Trial (Val-HeFT) randomized 5010 patients with NYHA class II–IV HF and a low LV ejection fraction to 160 mg valsartan daily or placebo.[91] Ninety-three percent of the patients were treated with ACE inhibitors, 85% with diuretics, 67% with digoxin, and 35% with beta blockers.

At 23-month follow up, mortality was similar in the 2 treatment groups.[91] Mortality plus morbidity was significantly reduced 13% in patients treated with valsartan. Valsartan significantly reduced mortality in patients treated with neither an ACE inhibitor or beta blocker.[91]

The Valsartan in Acute Myocardial Infarction (VALIANT) trial randomized 14,703 patients after MI complicated by LV systolic dysfunction, HF, or both to 160 mg valsartan twice daily, 80 mg valsartan twice daily plus 50 mg captopril 3 times daily, or 50 mg captopril 3 times daily.[92] At 25-month median follow up, all-cause mortality was similar in the 3 groups. Hypotension and renal dysfunction were more common in patients treated with valsartan, whereas cough, rash, and taste disturbance were more common in patients treated with captopril.[92] Combining valsartan with captopril increased the incidence of adverse effects without improving survival.[92]

In the Candesartan in Heart failure: Assessment of Reduction in Mortality and morbidity (CHARM)–Alternative study, 2028 patients with HF and a low LV ejection fraction who were intolerant to ACE inhibitors were randomized to 32 mg candesartan once daily or placebo.[93] At 34-month median follow up, candesartan significantly reduced the incidence of cardiovascular death or hospitalization for HF by 30%.[93]

In the CHARM–Added study, 2548 patients with HF and a low LV ejection fraction treated with ACE inhibitors were randomized to 32 mg candesartan daily or to placebo.[94] At 41-month median follow up, addition of candesartan to the ACE inhibitor significantly reduced cardiovascular death or hospitalization for HF by 15%.[94]

In the CHARM–Preserved study, 3023 patients with diastolic HF were randomized to 32 mg candesartan daily or to placebo.[95] At 37-month median follow up, candesartan insignificantly reduced cardiovascular death or hospitalization for HF by 11%.[95] On the basis of data from these 6 studies,[90–95] the author concurs with the ACC/AHA guidelines[1] that an angiotensin receptor blocker should be used for treating HF if the patient cannot tolerate an ACE inhibitor because of cough, angioneurotic edema, rash, or altered taste sensation.

Beta Blockers

Chronic administration of beta blockers after MI reduces mortality, sudden cardiac death, and recurrent MI, especially in elderly persons.[96,97] These benefits are more marked in patients with a history of HF.[98]

Beta blockers have been documented to reduce mortality in elderly persons with complex ventricular arrhythmias associated with prior MI and low[99] or normal[100] LV ejection fraction (EF). In patients with prior MI, low LVEF, and complex ventricular arrhythmias, beta blockers caused a significant 32% decrease in occurrence of new or worsened HF.[99] The benefit of beta blockers in decreasing coronary events in elderly patients with prior MI is also especially increased in patients with diabetes mellitus,[101] peripheral arterial disease,[102] and low LV ejection fraction.[68,103] Beta blockers are effective in significantly reducing mortality in elderly patients with HF associated with low[104–107] or normal[108] LV ejection fraction (Table 11).

Beta blockers are effective in antagonizing neurohormonal systems that cause myocyte apoptosis, myocyte necro-

TABLE 11. Effect of Beta-Adrenergic Blockers on Mortality in Patients With Heart Failure in Placebo-Controlled Trials

Study	Results
Packer M, et al[104] (n = 1094)	At 6- to 12-mo follow up of persons with NYHA class II, III, or IV HF and low LVEF, compared with placebo, carvedilol significantly decreased mortality 65%
CIBIS II[105] (n = 2647)	At 1.3-yr follow up of persons with NYHA class III or IV HF and low LVEF, compared with placebo, bisoprolol significantly decreased mortality 34%
MERIT-HF[106] (n = 3991)	At 1-yr follow up of persons with NYHA class II, III, or IV HF and low LVEF, compared with placebo, metoprolol CR/XL significantly decreased mortality 34%
COPERNICUS[107] (n = 2289)	At 10.4-mo follow up of patients with severe HF and low LVEF, compared with placebo, carvedilol significantly reduced mortality 35%

NYHA indicates New York Heart Association; HF, heart failure; LVEF, left ventricular ejection fraction.

sis, myocyte hypertrophy, fetal gene program activation, extracellular matrix alterations, and beta receptor uncoupling.[109] Beta blockers may prevent or reverse increased systemic vascular resistance and increased afterload caused by excessive sympathetic nervous system activation. Beta blockers also decrease levels of atrial natriuretic peptide, brain natriuretic peptide, and tumor necrosis alpha levels.[110] Beta blockers are also effective in preventing cardiovascular events because of their antihypertensive, antiischemic, antiarrhythmic, and antiatherogenic[111] effects.

By slowing the ventricular rate to less than 90 beats/min, thereby increasing LV diastolic filling time and causing an increase in LV end-diastolic volume, by reducing myocardial ischemia, by decreasing elevated blood pressure, by decreasing LV mass, and by improving LV relaxation, beta blockers are also beneficial in the treatment of patients with diastolic HF. Beta blockers are well tolerated in these patients despite sinus bradycardia at rest. The increase in ventricular rate that occurs after exercise can also be prevented with modest doses of beta blockers, especially in elderly patients.

Prospective, randomized studies have shown that beta blockers significantly reduce mortality in patients with HF associated with low[104–107] or normal[108] LV ejection fraction (Table 11). Beta blockers reduce all-cause mortality, cardiovascular mortality, sudden death, and death from worsening HF in patients with HF.[104–108] Beta blockers significantly reduce mortality in blacks[104,106,107] and in whites[104–108] with HF, in women[104–108] and in men[104–108] with HF, in elderly[104–108] and in younger[104–107] patients with HF, in patients with diabetes[104–108] and in nondiabetics[104–108] with HF, and in patients with severe HF[104–107] and with mild or moderate HF.[104–108] Beta blockers should be used to treat patients with HF and low LV ejection fraction[104–107] (Table 6) or normal LV ejection fraction[108] (Table 7) unless there are contraindications to their use. Carvedilol and metoprolol CR/XL are the only beta blockers that have been approved by the U.S. Food and Drug Administration for the treatment of HF in the United States. Bisoprolol is also approved for the treatment of HF in Europe.

Patients with prior MI and asymptomatic low LV ejection fraction should be treated with ACE inhibitors plus beta blockers.[1,68,112,113] An observational prospective study was performed in 477 patients (196 men and 281 women), mean age 79 years, with prior MI and low LV ejection fraction (mean LV ejection fraction of 31%).[68] Compared with no beta blocker or ACE inhibitor, at 34-month follow up, ACE inhibitors alone significantly reduced new coronary events 17% and new HF 32%, and beta blockers alone significantly reduced new coronary events 25% and new HF 41%.[68] Compared with no beta blocker or ACE inhibitor, at 41-month follow up, ACE inhibitors plus beta blockers significantly reduced new coronary events 37% and new HF 61%.[68] The significantly longer follow-up time in patients treated with ACE inhibitors plus beta blockers indicates that beta blockers plus ACE inhibitors delayed as well as reduced the occurrence of new coronary events and HF.[68]

Patients should be treated with an ACE inhibitor or angiotensin receptor blocker and be in a relatively stable condition without the need of intravenous inotropic therapy and without signs of marked fluid retention before initiating beta blocker therapy in patients with HF.[114] Beta blockers should be initiated in a low dose such as 3.125 mg carvedilol mg twice daily or 12.5 mg metoprolol CR/XL daily if there is NYHA class III or IV HF or 25 mg daily if there is NYHA class II HF. The dose of beta blockers should be doubled at 2- to 3-week intervals with the maintenance dose of beta blockers reached over 3 months (25 mg carvedilol twice daily or 50 mg twice daily if over 187 lbs or metoprolol 200 mg CR/XL once daily). The patient may experience fatigue during the initiation or uptitration of the dose of beta blockers with this effect dissipating over time. The need to continue beta blockers in this patient must be stressed because of the importance of beta blockers in reducing mortality.

During titration, the patient should be monitored for HF symptoms, fluid retention, hypotension, and bradycardia.[114] If there is worsening of symptoms, increase the dose of diuretics or ACE inhibitors. Temporarily reduce the dose of beta blockers if necessary. If there is hypotension, reduce the dose of vasodilators and temporarily reduce the dose of beta blockers if necessary. Reduce or discontinue drugs that may decrease heart rate in the presence of bradycardia. Contraindications to the use of beta blockers in patients with HF are bronchial asthma, severe bronchial disease, symptomatic bradycardia, and symptomatic hypotension.[114]

Aldosterone Antagonists

At 2-year follow up of 1663 patients, mean age 65 years, with severe HF and a low LV ejection fraction treated with diuretics, ACE inhibitors, 73% with digoxin, and 10% with beta blockers, 25 mg spironolactone daily significantly

reduced mortality 30% and hospitalization for worsening HF by 35%.[115] At 16-month follow up of 6632 patients, mean age 64 years, with acute myocardial infarction complicated by HF and a low LV ejection fraction treated with diuretics, ACE inhibitors, and 75% with beta blockers, 50 mg eplerenone daily significantly reduced mortality 15% and death from cardiovascular causes or hospitalization for cardiovascular events by 13%.[116]

The ACC/AHA guidelines recommend using aldosterone antagonists in patients with class IV HF and low LV ejection fraction despite treatment with diuretics, ACE inhibitors, beta blockers, and digoxin if there is preserved renal function and a normal serum potassium with a class II_a recommendation (Table 6).[1]

Prospective, double-blind, randomized studies need to be performed to investigate the effect of aldosterone antagonists on mortality and hospitalization for HF in patients with diastolic HF because modulation of the renin–angiotensin–aldosterone system may affect fibroblast activity, interstitial fibrosis, intracellular calcium handling, and myocardial stiffness.

Isosorbide Dinitrate Plus Hydralazine

Oral nitrates reduce preload and reduce pulmonary congestion in patients with HF. Hydralazine reduces afterload, improving perfusion at the same level of LV filling pressure. In the Veterans Administration Cooperative Vasodilator–Heart Failure Trial I, compared with placebo, oral isosorbide dinitrate plus hydralazine significantly reduced mortality 38% at 1 year, 25% at 2 years, and 23% at 3 years in men, mean age 58 years, with abnormal LV ejection fraction.[117] In 83 patients with a normal LV ejection fraction in this study, compared with placebo, isosorbide dinitrate plus hydralazine insignificantly decreased mortality 41% from a 9.0% annual mortality rate to a 5.3% annual mortality rate.[118]

The African-American Heart Failure Trial (A-HeFT) randomized 1040 blacks with HF and a low LVEF (only 23% with ischemic heart disease) treated with diuretics, ACE inhibitors, and beta blockers to isosorbide dinitrate plus hydralazine or to placebo.[72] At 10-month follow up, isosorbide dinitrate plus hydralazine significantly reduced mortality by 43% and rate of first hospitalization for HF by 33%.[72]

The ACC/AHA guidelines recommend using isosorbide dinitrate plus hydralazine in patients with HF who are being treated with diuretics and beta blockers, and who cannot be given an ACE inhibitor or angiotensin receptor blocker because of hypotension or renal insufficiency with a class II_a recommendation (Table 6).[1] Oral nitrates plus hydralazine should also be considered for the treatment of diastolic HF in elderly patients with persistent symptoms of HF despite diuretics, beta blockers, and ACE inhibitors (Table 7).

The initial dose of oral isosorbide dinitrate in elderly patients with HF is 10 mg 3 times daily with subsequent titration up to a maximum dose of 40 mg 3 times daily. Nitrates should be given no more than 3 times daily, with daily nitrate washout intervals of 12 hours to prevent nitrate tolerance from developing. The initial dose of oral hydralazine in elderly patients with HF is 10 to 25 mg 3 times daily with subsequent titration up to a maximum dose of 100 mg 3 times daily.

Digoxin

Digoxin reduces the rapid ventricular rate associated with supraventricular tachyarrhythmias and may be used to treat older patients with HF and supraventricular tachyarrhythmias such as atrial fibrillation. However, digoxin should not be used to treat patients with HF in sinus rhythm with diastolic HF. By increasing contractility through increased intracellular calcium concentration, digoxin may increase LV stiffness in these patients, increasing LV filling pressure and aggravating HF associated with normal LV ejection fraction.[119,120]

At 37-month follow up of 7788 patients, mean age 64 years, with HF (6800 with a LV ejection fraction $\leq$45% and 988 with a LV ejection fraction $>$45%) in the Digitalis Investigator Group (DIG) study, mortality was similar in patients treated with digoxin or placebo in patients with low or normal LV ejection fraction.[121,122] HF hospitalization was significantly reduced 28% in patients with a low LV ejection fraction and insignificantly reduced 21% in patients with a LV ejection fraction $>$45%.[122] Hospitalization for any cause was significantly reduced 8% in patients with a low LV ejection fraction and insignificantly increased 4% in patients with a LV ejection fraction $>$45%.[122] Hospitalization for suspected digoxin toxicity in patients treated with digoxin was 0.67% in patients aged 50 to 59 years, 1.91% in patients aged 60 to 69 years, 2.47% in patients aged 70 to 79 years, and 4.42% in patients aged $\geq$80 years.[122]

A post hoc subgroup analysis of data from women with a LV ejection fraction $<$45% in the DIG study showed by multivariate analysis that digoxin significantly increased the risk of death among women by 23% (absolute increase of 4.2%).[123] A post hoc subgroup analysis of data from men with a LV ejection fraction $<$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 $\geq$1.2 ng/mL.[124]

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.[125] This retrospective analysis also showed that higher NYHA classes were associated with poorer outcomes in patients with diastolic HF.[126]

On the basis of these data, women with systolic or diastolic HF and men with diastolic HF (Table 7) should not be treated with digoxin. Men with symptoms of persistent HF despite treatment with diuretics, ACE inhibitors, and beta blockers and a low LV ejection fraction should be treated with digoxin (Table 6).[1] The maintenance dose of digoxin should be 0.125 mg daily in elderly men and the serum digoxin level should be between 0.5 and 0.8 ng/mL.

Digoxin has a narrow therapeutic index, especially in elderly patients. Age-related reduction in renal function increases serum digoxin levels in older persons. The decrease in skeletal muscle mass in elderly patients reduces the volume

of distribution of digoxin, increasing serum digoxin levels. Elderly patients are also more likely to be taking drugs that interact with digoxin by interfering with its bioavailability or excretion. For example, spironolactone, triamterene, amiodarone, quinidine, verapamil, propafenone, erythromycin, tetracycline, propantheline, and other drugs increase serum digoxin levels. Therefore, elderly patients receiving these drugs are at increased risk for developing digitalis toxicity.[127] In addition, hypokalemia, hypomagnesemia, myocardial ischemia, hypoxia, acute and chronic lung disease, acidosis, hypercalcemia, and hypothyroidism may cause digitalis toxicity despite normal serum digoxin levels.[127]

Other Neurohormonal Antagonists

Natriuretic peptides are extensively reviewed elsewhere.[128] Omapatrilat is a dual inhibitor of both ACE and neutral endopeptidase.[129,130] At 15-month follow up of patients, mean age 63 years, with NYHA class II–IV HF and low LV ejection fraction, compared with enalapril, omapatrilat was not significantly more effective than enalapril in reducing the risk of death or hospitalization for HF requiring intravenous therapy.[130] In patients with class II or III HF and low LV ejection fraction, the endothelin-A/endothelin-B antagonist enrasentan added to standard therapy for HF did not improve clinical status, was associated with worsening clinical status and outcome, and was not well tolerated in comparison with placebo.[131]

Two trials of the antitumor necrosis factor agent etanercept investigating its effect on mortality and morbidity in patients with HF and low LV ejection fraction were also discontinued because of futility.[132] A trial using an antitumor necrosis factor chimeric monoclonal antibody infliximab was also discontinued because of higher rates of mortality and hospitalization in the infliximab-treated group.[132] However, preliminary data with arginine vasopressin antagonists in the treatment of patients with HF are encouraging and warrant further investigation.[133,134]

Calcium Channel Blockers

Calcium channel blockers such as nifedipine, diltiazem, and verapamil exacerbate HF in patients with HF and low LV ejection fraction.[135] Diltiazem significantly increased mortality in patients with pulmonary congestion and abnormal LV ejection fraction after MI.[136] The Multicenter Diltiazem Postinfarction Trial also showed in patients with a LV ejection fraction $<40\%$ that late HF at follow up was significantly increased in patients randomized to diltiazem (21%) compared with patients randomized to placebo (12%).[137]

The vasoselective calcium channel blockers amlodipine[138] and felodipine[139] did not significantly affect survival in patients with HF and abnormal LV ejection fraction. In these studies, there was a significantly higher incidence of pulmonary edema in patients treated with amlodipine[138] (15%) than in patients treated with placebo (10%) and a significantly higher incidence of peripheral edema in patients treated with amlodipine[138] or felodipine[139] than in those treated with placebo. On the basis of the available data, calcium channel blockers should not be administered to patients with HF and an abnormal LV ejection fraction (Table 6).[1]

However, in a double-blind, 5-week crossover trial in 20 men with HF and normal LV ejection fraction, compared with placebo, verapamil improved exercise capacity, peak LV filling rate, and a clinicoradiographic heart failure score.[140] Calcium channel blockers may be given to patients with diastolic HF and symptoms despite diuretics, beta blockers, ACE inhibitors, and isosorbide dinitrate plus hydralazine (Table 7).

SYNCHRONIZED PACING AND CARDIOVERTER–DEFIBRILLATORS

Approximately one third of patients with chronic HF have electrocardiographic evidence of a major intraventricular conduction delay, which may worsen LV systolic dysfunction through asynchronous ventricular contraction.[141] Cardiac resynchronization therapy (CRT) achieved through atrial-synchronized biventricular pacing has been shown to cause significant clinical improvement in patients with moderate- to-severe HF, a low LV ejection fraction, and a QRS duration on the resting ECG of 120 ms or more.[141–143] At 1-year follow up of 1520 patients, mean age 67 years, with NYHA class III or IV HF and a QRS duration on the resting ECG of 120 ms or more, compared with medical therapy alone, all-cause mortality was insignificantly reduced 24% by CRT and significantly reduced 36% by CRT plus implantable cardioverter–defibrillator (ICD) therapy.[143]

At 29-month follow up of 813 patients with class III or IV HF, a low LV ejection fraction, and cardiac dyssynchrony, compared with medical therapy alone, CRT significantly reduced death or unplanned hospitalization for a major cardiovascular event by 37% and mortality by 36%.[144] In the Sudden Cardiac Death in Heart Failure Trial (SCD-HEFT), 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 electrocardiogram (ECG) of 120 ms, were randomized to placebo, amiodarone, or an ICD.[145] At 46-month median follow up, compared with placebo, amiodarone insignificantly increased mortality by 6%.[145] At 46-month median follow up, compared with placebo, ICD therapy significantly reduced all-cause mortality by 23%.[145]

On the basis of these data, CRT plus ICD therapy should be considered in elderly patients with severe CHF despite optimal medical therapy resulting from ischemic or nonischemic heart disease associated with a LV ejection fraction of 35% or less with limited exercise capacity, preferably in sinus rhythm, and with evidence of ventricular dyssynchrony. Unlike the QRS duration on the ECG, the magnitude of basal ventricular dyssynchrony assessed by echocardiography, tissue Doppler, or by magnetic resonance-tagged imaging is a better predictor of outcome.[141]

At 3.7-year follow up of 535 patients, mean age 70 years, who had an ICD, all-cause mortality was significantly increased in patients with concomitant dual-chamber rate responsive pacing at 70 beats/min (DDDR-70) (19% of 264 patients) compared with patients with backup ventricular

pacing at 40 beats/min (VVI-40) (11% of 271 patients).[146] At follow up, patients treated with DDDR-70 pacing had a significant decrease in LV ejection fraction and a significant increase in new LV wall motion abnormality compared with patients treated with backup VVI-40 pacing.[147] Concomitant DDDR-70 pacing in patients with ICDs without an indication for antibradycardia pacing is deleterious.

INOTROPIC THERAPY

Phosphodiesterase inhibitors such as milrinone,[148] flosequinan,[149] enoximone,[150] vesnarinone,[151] and pimobendan[152] have been demonstrated to significantly increase mortality in patients with HF and low LV ejection fraction. Mortality was significantly increased 21% by 60 mg vesnarinone daily and insignificantly increased 11% by 30 mg vesnarinone daily.[151]

Orally administered adrenergic agents have also not been beneficial in the treatment of patients with HF and low LV ejection fraction. Xamoterol, a beta-1 selective partial agonist, significantly increased mortality 2.5 times in comparison with placebo in patients with HF and abnormal LV ejection fraction.[153] Ibopamine, an oral dopaminergic agonist, that causes peripheral and renal vasodilation, significantly increased mortality 26% in comparison with placebo in patients with HF and low LV ejection fraction.[154] The prostaglandin epoprostenol administered intravenously to patients with severe HF and low LV ejection fraction also significantly increased mortality in the Flolan International Randomized Trial (FIRST) study.[155]

Intravenous administration of the beta-adrenergic agonist dobutamine can cause short-term clinical and hemodynamic improvement in persons with HF and low LV ejection fraction. However, arrhythmic events are common in older persons with HF treated with intravenous dobutamine.[156] There are also data suggesting increased ventricular arrhythmias and mortality with use of long-term intermittent therapy with intravenous dobutamine administration to patients with HF and abnormal LV ejection fraction.[157] An analysis of patients with HF receiving continuous intravenous dobutamine in the FIRST study found that dobutamine use was an independent predictor of mortality with no associated improvement in quality of life.[155] However, preliminary data have shown in 36 patients that the addition of intermittent levosimendan infusions prolonged the 45-day survival of patients with advanced HF refractory to intermittent dobutamine infusions.[158]

NESIRITIDE

Intravenous nesiritide (human B-type natriuretic peptide) causes hemodynamic and symptomatic improvement in hospitalized patients with decompensated HF through balanced vasodilatory effects, neurohormonal suppression, and enhanced natriuresis and diuresis.[159,160] Nesiritide improved hemodynamic function and some self-reported symptoms more effectively than intravenous nitroglycerin or placebo in a randomized, double-blind trial of 489 patients with dyspnea at rest from decompensated HF in the Vasodilation in the Management of Acute CHF (VMAC) study.[159]

In 261 hospitalized patients with decompensated HF, 103 patients were randomized to 0.015 μg/kg/min nesiritide, 100 patients were randomized to 0.030 μg/kg/min nesiritide, and 58 patients were randomized to intravenous dobutamine.[160] Six-month mortality was 31% for the dobutamine-treated group, 18% for the lower-dose nesiritide-treated group, and 24% for the higher-dose nesiritide-treated group.[160] This trial was not powered for mortality. HF hospital readmission rate was 13% for the dobutamine-treated group, 4% for the lower-dose nesiritide-treated group, and 4% for the higher-dose nesiritide-treated group.[160] These data suggest that intravenous nesiritide is more efficacious than intravenous dobutamine in the treatment of patients hospitalized with acutely decompensated HF.

However, in the VMAC study, compared with intravenous nitroglycerin, intravenous nesiritide insignificantly increased hospital stay and 30-day and 6-month mortality.[159,161] This trial was also not powered for mortality. A review of U.S. Food and Drug Administration files available through the web site also showed that nesiritide significantly increases the risk of worsening renal function in patients with acute decompensated HF.[162] A review of U.S. Food and Drug Administration files available through the web site also found that nesiritide insignificantly increased mortality 1.8 times in patients with acute decompensated systolic HF.[163] The European Trial of Nesiritide in Acute Decompensated Heart Failure is randomizing 1900 patients with acute decompensated HF to treatment with nesiritide or placebo. This study should clarify the role of nesiritide in the treatment of patients with acute decompensated HF.

SURGICAL VENTRICULAR RESTORATION

Surgical ventricular restoration (SVR) was developed to restore ventricular size and shape to a more normal architecture. Anterior MI leads to change in ventricular shape and volume. In the absence of reperfusion, dyskinesia develops. Delayed reperfusion by angioplasty or by thrombolysis leads to akinesia. Both dyskinesia and akinesia lead to HF by dysfunction of the remote muscle.[164] Anterior ventricular endocardial restoration was associated with an 88% 18-month survival in 421 patients who had surgical anterior ventricular endocardial restoration plus coronary artery bypass graft surgery (CABGS) or mitral valve repair.[164] Freedom from hospital readmission for HF at 18-month follow up was 85%.[164] The Surgical Treatment of Ischemic Heart Failure Trial was recently started and is investigating long-term outcomes in patients with HF and low LV ejection fraction randomized to medical therapy, CABGS, or CABGS plus SVR.

END-STAGE HEART FAILURE

An implantable LV assist device (LVAD) has benefited patients with end-stage HF as a bridge to cardiac transplantation. However, cardiac transplantation is not a viable option for most of patients with end-stage HF. One hundred twenty-nine transplant-ineligible patients, mean age 67 years, with end-stage HF were randomized to medical therapy or to an LVAD.[165] The 1-year survival

rate was 52% in the LVAD-treated group versus 25% in the medical therapy-treated group.[163] The 2-year survival rate was 23% in the LVAD-treated group versus 8% in the medical therapy-treated group.[165] These data suggest using a LVAD as an alternative therapy in selected patients who are not candidates for cardiac transplantation. Other therapies for elderly patients with end-stage HF include continuous intravenous inotropic infusions for palliation and hospice care.[1]

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