Review Article

Drug Treatment of Systolic and of Diastolic Heart Failure in Elderly Persons

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Underlying causes, risk factors, and precipitating causes of heart failure (HF) should be treated. Patients with HF and an abnormal left ventricular ejection fraction (systolic HF) or normal left ventricular 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. Cardiac synchronized pacing should be considered in patients with severe systolic HF despite optimal medical therapy, with sinus rhythm, and with ventricular dyssynchrony.

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 80% of patients hospitalized with HF are older than 65 years (1). HF is not only the most common cause of hospitalization of older persons in the United States but is also the most costly with annual expenditures of more than $40 billion spent each year. 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 (2). At 43-month follow-up of 2902 elderly persons (926 men and 1976 women), mean age 81 years, HF developed in 27% of patients (3). Significant independent risk factors for the development of HF were male gender (risk ratio ¼ 1.4), hypertension (risk ratio ¼ 2.5), coronary artery disease (CAD) (risk ratio ¼ 4.0); diabetes mellitus (risk ratio ¼ 1.6), and age (risk ratio ¼ 1.05 for each 1-year increase in age) (3). In the Framingham Heart Study, the lifetime risk of developing HF at age 40 years was 21.0% for men and 20.3% for women (4).

HF may be associated with an abnormal (<50%) left ventricular ejection fraction (LVEF) (systolic HF) or with a normal (≥50%) LVEF (diastolic HF). Although the terms systolic HF and diastolic HF are widely used and have been adopted in American and European practice guidelines, some authors prefer to use the terms HF with impaired or preserved systolic function.

The prevalence of diastolic HF increases with age and is higher in older women than in older men (3,5). In 674 persons with HF, mean age 81 years, 38% of men and 57% of women had diastolic HF (3). In 73 patients with HF, mean age 73 years, in the Framingham Heart Study, the prevalence of diastolic HF was 51% (6). In 269 patients, mean age 74 years, in the Cardiovascular Health Study, the prevalence of diastolic HF was 63% (7). The pathophysiology for the increased prevalence of diastolic HF in elderly persons is discussed in detail elsewhere (8).

The incidence of chronic atrial fibrillation increases with age (9). 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.

In 566 elderly HF patients, the 1-year mortality was 19% in patients with diastolic HF and 41% in patients with systolic HF (10). The 5-year mortality was 74% in patients with diastolic HF and 92% in patients with systolic HF (10). Elderly patients with HF and atrial fibrillation had a higher mortality than those with sinus rhythm (11). In 170,239 Medicare patients with HF, only 19% of black men, 16% of white men, 25% of black women, and 23% of white women survived 6 years (12).

There is an unsolved controversy between rhythm and ventricular rate control in patients with HF and atrial fibrillation (13). Several studies are ongoing that will provide more insight into the management of these patients.

Stages of HF

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 disorders strongly associated with the development of HF. 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 had symptoms or signs of HF (1). These patients have a prior myocardial infarction (MI), LV hypertrophy or fibrosis, LV dilatation or hypococontractility, 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 require specialized interventions (1).

TREATMENT OF STAGE A HF

In patients with stage A HF, treat hypertension (1,14–16), treat dyslipidemia (1,17–26), encourage regular exercise, encourage the avoidance of smoking, alcohol consumption, and illicit drug use, slow the ventricular rate in patients with supraventricular tachyarrhythmias, and use ACE inhibitors in patients with atherosclerotic vascular disease, diabetes mellitus, or hypertension (1). Diabetics should be treated as if they had CAD (27,28). Educational programs may have to be used to increase the use of lipid-lowering drugs (29,30).

TREATMENT OF STAGE B HF

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

GENERAL MEASURES FOR TREATMENT OF STAGE C HF

Comorbidities have a major role in the progression or recurrences of HF, and, in turn, can be worsened by HF itself (31). For example, anemia is emerging as a major risk factor for poor HF control (32). Observational databases and clinical trials suggest that anemia is an independent risk factor for adverse outcomes in patients with HF (33). Anemia also contributes to exercise intolerance which is a major morbidity in patients with chronic HF. Potential benefits of treating anemia with recombinant human erythropoietin include improved oxygen delivery, improved exercise capacity, attenuation of adverse LV remodeling, and reduction of apoptosis. Potential risks of this treatment include hypertension, increased thrombosis, platelet activation, and endothelial activation. Multiple ongoing studies will provide data on the relative benefits and risks of treating anemia with recombinant human erythropoietin in patients with chronic HF.

Other comorbidities in elderly patients with chronic HF include renal insufficiency, which worsens symptoms and prognosis and which may be aggravated by diuretics and ACE inhibitors. Treatment of elderly patients with HF with coexistent diabetes mellitus, chronic obstructive lung disease, and arthritis is extensively discussed elsewhere (34).

Cognitive dysfunction interferes with compliance with drugs, diet, and activity (35). Depression and social isolation worsen the prognosis and interfere with compliance (35). Postural hypotension and falls are exacerbated by diuretics, vasodilators, and beta blockers (36). Urinary incontinence is aggravated by diuretics. Sensory deprivation interferes with compliance. Nutritional disorders are aggravated by dietary restrictions. Polypharmacy may lead to adverse drug interactions. Frailty worsens symptoms and quality of life, is exacerbated by hospitalization, and leads to an increased risk of falls.

Underlying causes of HF should be treated when possible. Precipitating causes of HF should be identified and treated. Common precipitating factors of HF include dietary sodium excess, excess fluid intake, inadequate treatment, nonadherence to appropriate drugs, uncontrolled hypertension, anemia, infection, fever, hypoxia, a hot, humid environment, bradyarrhythmias, tachyarrhythmias, myocardial ischemia or infarction, pulmonary embolism, renal insufficiency, hyperthyroidism, hypothyroidism, and use of inappropriate drugs such as nonsteroidal anti-inflammatory drugs (NSAIDs). Hypertension should be treated with diuretics, ACE inhibitors, and beta blockers. Myocardial ischemia should be treated with nitrates and beta blockers.

Elderly 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 revascularization 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. Infective endocarditis should be treated with intravenous antibiotics and with surgical replacement of valvular lesions if clinically indicated (37). 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 two-dimensional echocardiography. The dose of warfarin administered should achieve an International Normalized Ratio of 2.0–3.0.

Patients with HF should have their sodium intake decreased to 1.6 grams of sodium (4 grams of sodium chloride) daily. Excessive fluid intake should be avoided. 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 (38). A multidisciplinary approach to care is useful (35,39).
Diuretics

Diuretics are the first-line drug in the treatment of elderly patients with HF and volume overload (Tables 1 and 2). A thiazide diuretic such as hydrochlorothiazide may be used to treat elderly patients with mild HF. However, a thiazide diuretic is ineffective if the glomerular filtration rate is less than 30 ml/min. Elderly 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. Elderly 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.

Elderly patients with diuretic-treated HF need close monitoring of their serum electrolytes. Hypokalemia and hypomagnesemia, both of which may precipitate ventricular arrhythmias and digitalis toxicity, may develop. Hypokalemia 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. Elderly patients with systolic or diastolic HF and volume overload should be treated with diuretics. However, elderly patients with systolic HF tolerate higher doses of diuretics than do elderly patients with diastolic HF. Elderly patients with diastolic HF require high LV filling pressures to maintain an adequate stroke volume and cardiac output, and cannot tolerate intravascular depletion. Therefore, older patients with diastolic HF should be treated with cautious use of a low sodium diet rather than with large doses of diuretics. The dose of diuretics should be gradually reduced and stopped if possible when fluid retention is not present in patients with diastolic or systolic HF. It has been found that patients on high doses of diuretics had an increased mortality (42).

A meta-analysis of randomized controlled trials found that compared to placebo, diuretics reduced the risk of death and worsening HF in patients with HF (43). However, there are data which showed that diuretic-induced electrolyte disturbances may result in fatal arrhythmias in patients with systolic HF (44).

ACE Inhibitors

ACE inhibitors improve symptoms, quality of life, and exercise tolerance in patients with HF. ACE inhibitors also have been found to significantly increase survival in patients with systolic HF at long-term follow-up by 27% (45), by 28% (46), by 16% (47), and by 27% (48) and should be used to treat patients with systolic HF (Table 1) (1). ACE inhibitors also improve survival and reduce the incidence of HF and coronary events in patients with abnormal LVEF without HF (49–52) 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 LVEF, and in LV diastolic function assessed by Doppler echocardiography (53). Enalapril also significantly decreased cardiothoracic ratio measured from chest x-rays and echocardiographic LV mass (50). In an observational study of 539 patients (55% women), mean age 75 years, with diastolic HF, at 6-month follow-up, ACE inhibitors decreased mortality and improved quality-of-life scores (54). On the basis of these limited data (53,54), elderly persons with diastolic HF should be treated with ACE inhibitors (Table 2).

ACE inhibitors should be started in elderly persons with HF in low doses after correction of hyponatremia or volume depletion. It is important to avoid overdiuresis before initiating 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. Patients with HF
should be treated with high doses of ACE inhibitors (for example, 32.5–35 mg of lisinopril daily) unless low doses (for example, 2.5–5 mg of lisinopril daily) are the only doses that can be tolerated (55).

Elderly 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 on ACE inhibitors to detect increases in blood urea nitrogen and in serum creatinine, especially in elderly patients with renal artery stenosis. A doubling in serum creatinine or an increase in serum creatinine of 0.5 mg/dl or higher should cause the physician to consider renal dysfunction caused by ACE inhibitors, a need to decrease 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. Serum potassium needs to be monitored carefully in patients with systolic HF treated with both an ACE inhibitor and aldosterone antagonist.

Asymptomatic hypotension with a systolic blood pressure between 80 and 90 mmHg 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.

There are conflicting data about the importance of the negative interaction of aspirin with ACE inhibitors in the treatment of patients with HF and CAD or other atherosclerotic vascular disease. In a study of elderly patients with HF treated with ACE inhibitors, aspirin significantly reduced mortality 31% (56).

Until data from controlled clinical trials are available, a prudent approach to this controversy might be to reduce the dose of aspirin to 80–100 mg daily or substitute clopidogrel as an antplatelet 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

Losartan significantly reduced the rate of hospitalization for HF in patients with type 2 diabetes mellitus and nephropathy (57) and in diabetics with hypertension and electrocardiographic LV hypertrophy (58). In the Losartan Heart Failure Survival Study II of 3152 patients aged ≥60 years with systolic HF, at 555-day follow-up, 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 (59).

Angiotensin receptor blockers have been shown to reduce mortality plus morbidity in patients with systolic HF who cannot tolerate ACE inhibitors because of cough, rash, altered taste sensation, or angioneurotic edema (60–62). 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 (Table 1) (1).

In the Candesartan in Heart failure: Assessment of Reduction in Mortality and morbidity—Preserved study, 3023 patients with diastolic HF were randomized to candesartan 32 mg daily or to placebo (63). At 37-month follow-up, candesartan insignificantly reduced cardiovascular death or hospitalization for HF by 11%, but significantly reduced hospitalization for HF (63). An angiotensin receptor blocker should be used for treating systolic or diastolic HF if the patient cannot tolerate an ACE inhibitor because of cough, angioneurotic edema, rash, or altered taste sensation (Tables 1 and 2).

Beta Blockers

Prospective randomized studies have shown that beta blockers significantly reduced mortality in patients with systolic HF at follow-up by 65% (64), by 34% (65), by 34% (66), and by 35% (67). Beta blockers significantly reduce all-cause mortality, cardiovascular mortality, sudden death, and death from worsening HF in patients with HF (64–68). Beta blockers significantly reduce mortality in African Americans and whites with HF, in women and men with HF, in elderly and in younger patients with HF, in diabetics and nondiabetics with HF, and in patients with severe, mild, or moderate HF (64–68). Beta blockers should be used to treat elderly patients with systolic HF (64–67) (Table 1) or diastolic HF (68) (Table 2) unless there are contraindications to their use. Beta blockers are useful in treating myocardial ischemia, hypertension, and excessive tachycardia in patients with diastolic HF.

Patients with prior MI and asymptomatic abnormal LV ejection fraction should be treated with ACE inhibitors plus beta blockers (1,52,69). An observational prospective study was performed in 477 patients, mean age 79 years, with prior MI and abnormal LVEF (52). Compared with no beta blocker or ACE inhibitor, at 34-month follow-up, ACE inhibitors alone significantly reduced new coronary events by 17% and new HF by 32%, and beta blockers alone significantly reduced new coronary events by 25% and new HF by 41% (52). Compared with no beta blocker or ACE inhibitor, at 41-month follow-up, ACE inhibitors plus beta blockers significantly reduced new coronary events by 37% and new HF by 61% (52).

Patients with HF 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 beginning beta blocker therapy (70). Beta blockers should be initiated in a low dose such as carvedilol 3.125 mg twice daily or metoprolol CR/XL 12.5 mg 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 (carvedilol 25 mg twice daily or 50 mg twice daily [if patient weighs more than 187 pounds].
or metoprolol CR/XL 200 mg once daily). The patient may experience fatigue or increased exertional dyspnea during the initiation or up-titration 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 (70). 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 diuretics 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 (70).

**Aldosterone Antagonists**

Spironolactone 25 mg daily has been found to decrease mortality and hospitalization for worsening HF in patients with severe HF (71). At 16-month follow-up of 6632 patients, mean age 64 years, with acute MI complicated by systolic HF, eplerenone 50 mg daily significantly decreased mortality 15% and death from cardiovascular causes or hospitalization for cardiovascular events by 13% (72). The ACC/AHA guidelines recommend using aldosterone antagonists in patients with class IV systolic HF despite treatment with diuretics, ACE inhibitors, beta blockers, and digoxin if there is preserved renal function and a normal level of serum potassium (Table 1).

**Isosorbide Dinitrate Plus Hydralazine**

In the Veterans Administration Cooperative Vasodilator-Heart Failure Trial I, compared with placebo, oral isosorbide dinitrate plus hydralazine significantly decreased mortality 38% at 1 year, 25% at 2 years, and 23% at 3 years in patients with systolic HF (73). In 83 nonelderly patients with diastolic HF in this study, compared with placebo, isosorbide dinitrate plus hydralazine insignificantly decreased mortality by 41% (74). At 10-month follow-up of African Americans with systolic HF, isosorbide dinitrate plus hydralazine significantly reduced mortality by 43% and rate of first hospitalization for HF by 33% (75).

The ACC/AHA guidelines recommend using isosorbide dinitrate plus hydralazine in patients with systolic 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 (Table 1) (1). Oral nitrates plus hydralazine should also be considered for the therapy of diastolic HF in elderly patients with persistent symptoms of HF despite diuretics, beta blockers, and ACE inhibitors (Table 2).

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 the development of nitrate tolerance. The initial dose of oral hydralazine in elderly patients with HF is 10–25 mg 3 times daily, with subsequent titration up to a maximum dose of 100 mg 3 times daily.

**Digoxin**

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 (76).

At 37-month follow-up of 7788 patients, mean age 64 years, with HF (6800 with systolic HF and 988 with diastolic HF) in the Digitalis Investigator Group (DIG study), mortality was similar in patients treated with digoxin or placebo (77,78). HF hospitalization was significantly reduced 28% in patients with systolic HF and insignificantly reduced 21% in patients with diastolic HF (78). All-cause hospitalization was significantly reduced 8% in patients with systolic HF and insignificantly increased 4% in patients with diastolic HF (78). Hospitalization for suspected digoxin toxicity in patients treated with digoxin was 0.67% in patients aged 50–59 years, 1.91% in patients aged 60–69 years, 2.47% in patients aged 70–79 years, and 4.42% in patients aged ≥80 years (78).

A post hoc subgroup analysis of data from women with systolic HF 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%) (79). A post hoc subgroup analysis of data from men with systolic HF in the DIG study showed that digoxin significantly reduced mortality by 6% if the serum digoxin level was 0.5–0.8 ng/ml, insignificantly increased mortality by 3% if the serum digoxin level was 0.8–1.1 ng/ml, and significantly increased mortality by 12% if the serum digoxin level was ≥1.2 ng/ml (80).

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 (81). This retrospective analysis also showed that higher NYHA classes were associated with poorer outcomes in patients with diastolic HF (82).

On the basis of these data, women with systolic or diastolic HF and men with diastolic HF (Tables 1 and 2) should not be treated with digoxin. Men with persistent symptoms due to systolic HF despite treatment with diuretics, ACE inhibitors, and beta blockers should be treated with digoxin (Table 1) (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 decrease in renal function increases serum digoxin levels in elderly 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 (80). 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 (83).

**Calcium Channel Blockers**

Calcium channel blockers such as nifedipine, diltiazem, and verapamil exacerbate systolic HF (84). Diltiazem significantly increased mortality in patients with pulmonary congestion and abnormal LVEF after MI (85). The Multicenter Diltiazem Postinfarction Trial also showed in patients with an LVEF <40% that late HF at follow-up was significantly increased in patients randomized to diltiazem (21%) compared with patients randomized to placebo (12%) (86).

The vasoselective calcium channel blockers amiodipine (87) and felodipine (88) did not significantly affect survival in patients with systolic HF. In these studies, there was a significantly higher incidence of pulmonary edema in patients treated with amiodipine (15%) than in patients treated with placebo (10%) and a significantly higher incidence of peripheral edema in patients treated with amiodipine or felodipine than in those treated with placebo. On the basis of the available data, calcium channel blockers should not be given to patients with systolic HF (Table 1) (1).

However, in a double-blind, 5-week crossover trial in 20 men with diastolic HF, compared with placebo, verapamil improved exercise capacity, peak LV filling rate, and a clinicoradiographic HF score (89). Calcium channel blockers may be prescribed to patients with diastolic HF and symptoms despite diuretics, beta blockers, ACE inhibitors, andisosorbide dinitrate plus hydralazine (Table 2).

**Synchronized Pacing and Cardioverter-Defibrillators**

Approximately one third of patients with chronic HF have electrocardiographic (ECG) evidence of a major intraventricular conduction delay which may worsen LV systolic dysfunction through asynchronous ventricular contraction. Cardiac resynchronization therapy (CRT) achieved through atrial-synchronized biventricular pacing has been shown to cause significant clinical improvement in patients with moderate-to-severe systolic HF and a QRS duration on the resting ECG of 120 ms or more (90). At 29-month follow-up of 813 patients with class III or IV systolic HF and cardiac dyssynchrony, compared to medical therapy alone, CRT significantly decreased death or unplanned hospitalization for a major cardiovascular event 37% and mortality 36% (91).

At 46-month follow-up of 2521 patients, mean age 60 years, with NYHA class II or III systolic HF and a mean QRS duration on the resting ECG of 120 ms in the Sudden Cardiac Death in Heart Failure Trial, compared with placebo, amiodarone insignificantly increased mortality by 6%, and implantable cardioverter-defibrillator (ICD) therapy significantly reduced all-cause mortality by 23% (92). Concomitant dual-chamber rate-responsive pacing at 70/minute in patients with ICDs without an indication for antibradyarrhythmia pacing is deleterious (93,94).

On the basis of these data, CRT plus ICD therapy should be considered in elderly patients with systolic HF and an LVEF <35% despite optimal medical therapy in sinus rhythm, and with evidence of ventricular dyssynchrony. However, CRT has been ineffective in treating systolic HF in 35% of patients, and the rate of unsuccessful implants ranges from 8% to 13%. CRT has not been investigated in patients with diastolic HF and would be unlikely to benefit these patients.

**Inotropic Therapy**

Phosphodiesterase inhibitors such as milrinone, flosequinan, enoximone, vesnarinone, and pimobendan have significantly increased mortality in patients with systolic HF. Orally administered adrenergic agents have not been beneficial in treating patients with systolic HF. The prostaglandin epoprostenol, administered intravenously to patients with severe systolic HF, also significantly increased mortality in the Flolan International Randomized Survival Trial (FIRST) (95). An analysis of patients with HF receiving continuous intravenous dobutamine in the FIRST study showed that dobutamine use was an independent predictor of mortality with no associated improvement in quality of life (95). However, continuous intravenous inotropic infusions may be very useful in the treatment of elderly patients with end-stage HF for palliation and hospice care (1).

**Nesiritide**

Intravenous nesiritide (human B-type natriuretic peptide) is being used to treat patients with decompensated systolic HF. However, in 489 patients with dyspnea at rest from decompensated HF in the Vasodilation in the Management of Acute Congestive (VMAC) HF study, compared with intravenous nitroglycerin, intravenous nesiritide insignificantly increased hospital stay and 30-day and 6-month mortality (96). A review of Food and Drug Administration files available via the internet also found that nesiritide insignificantly increased mortality 1.8 times in patients with acute decompensated systolic HF (97).

**Levosimendan**

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 (98). However, the effect of levosimendan in the treatment of patients with acute decompensated HF needs to be clarified by mortality data in placebo-controlled studies.

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