

Heart failure update

Treatment of heart failure with a normal left ventricular ejection fraction in the elderly

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Heart failure (HF) affects approximately 5 million persons in the United States; more than 550,000 new cases of HF are reported each year. Prevalence of HF with a normal left ejection fraction increases with age and is higher in older women than older men. Both underlying and precipitating causes of HF should be treated when possible. Hypertension, especially isolated systolic hypertension, should be treated with diuretics, ACE inhibitors, and beta blockers. Myocardial ischemia should be treated with nitrates and beta blockers. Anemia should be treated, as should hyperthyroidism, hypothyroidism, and obstructive sleep apnea. Use of inappropriate drugs, such as nonsteroidal anti-inflammatory drugs, should be avoided. Coronary revascularization should be performed in selected individuals.

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ARBs • calcium channel blockers • digoxin • vasodilators

Hear failure (HF) affects approximately 5 million persons in the United States; more than 550,000 new cases of HF are reported each year.¹ HF (a general term which includes patients with acute and chronic HF) is predominantly a disease of the elderly: 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, it is also the most costly.¹

The prevalence of HF with a normal

left ventricular ejection fraction (LVEF), ie, diastolic dysfunction, increases with age and is higher in older women than in older men.^{2,3} In 674 persons with HF, mean age 81, 38% of men and 57% of women had HF with a normal LVEF.³ In 73 patients with HF, mean age 73, in the Framingham Heart Study, the prevalence of HF with a normal LVEF was 51%.⁴ In 269 patients, mean age 74, in the Cardiovascular Health Study, the prevalence of HF with a normal LVEF was 63%.⁵

The pathophysiology for the increased prevalence of HF with a normal LVEF in the elderly is discussed in detail elsewhere.⁶ This article will discuss the therapy of HF with a normal LVEF in the elderly.

Treating heart failure

Both underlying and precipitating causes of HF should be treated when possible. Underlying causes include etiologic causes of HF, such as coronary artery disease, hypertension, valvular heart disease, cardiomyopathies, diabetes mellitus, etc. Precipitating causes of HF include dietary sodium excess, excess fluid intake, inadequate treatment, nonadherence to appropriate drugs, use of inappropriate drugs (such as nonsteroidal anti-inflammatory drugs [NSAIDs]), uncontrolled hypertension, anemia, fever, infection, hypoxia, hot and/or humid environment, alcohol, bradyarrhythmias, tachyarrhythmias, pulmonary embolism, MI or myocardial ischemia, renal insufficiency, hypothyroidism, or hyperthyroidism.

The table shows the management of elderly patients with HF and a normal LVEF. Hypertension, especially isolated systolic hypertension, hyperlipidemia, myocardial ischemia, and anemia should be treated, as should hyperthyroidism, hypothyroidism, and obstructive sleep apnea.

► Hypertension should be treated

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with diuretics, ACE inhibitors, and beta blockers. Treating with statins improves survival in both ischemic heart disease and nonischemic heart disease; it may do this by reducing inflammation.

► Myocardial ischemia should be treated with nitrates and beta blockers.

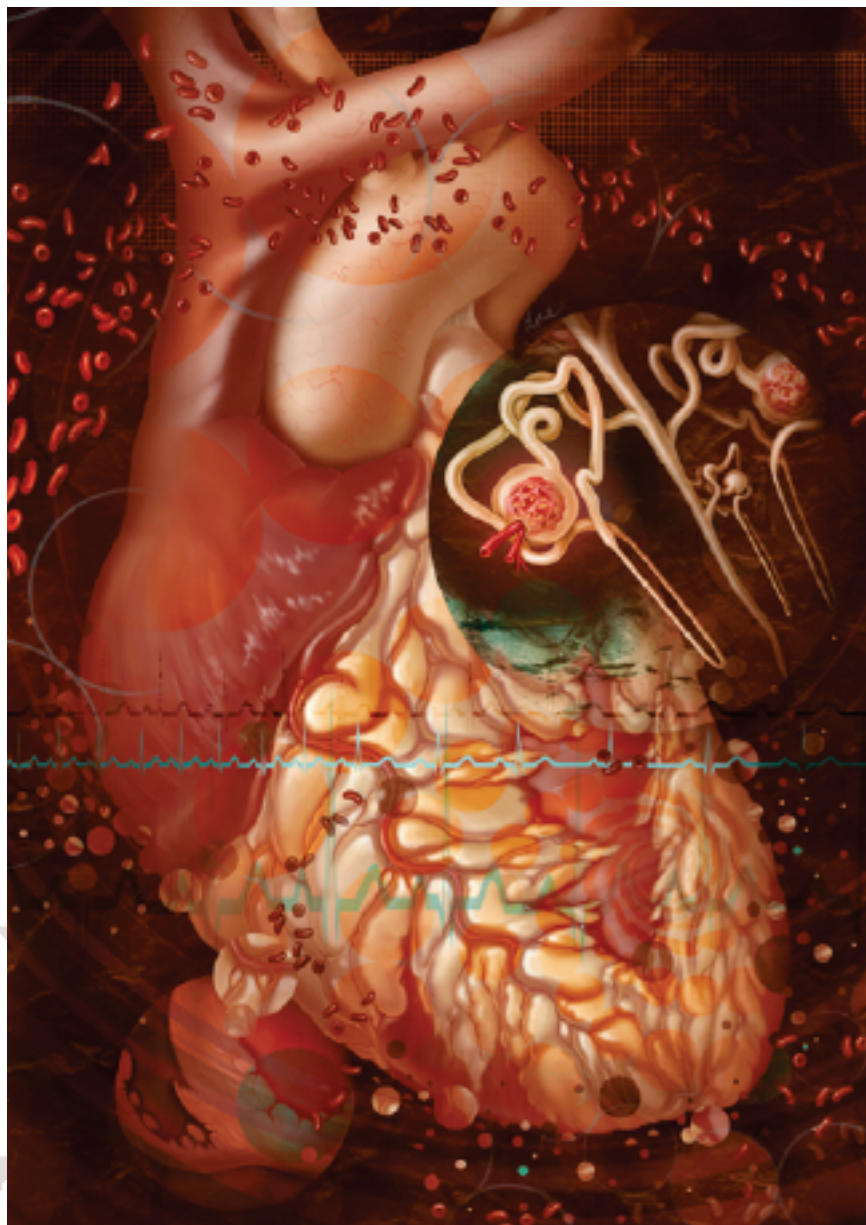
► Use of inappropriate drugs, such as NSAIDs, should be avoided in these patients. Patients with arthritis and HF could be treated with large doses of aspirin or acetaminophen for pain relief. Topical analgesics, such as capsaicin cream or methylsalicylate, may be used as adjunctive therapy. Intra-articular injection of hyaluronic acid may be useful in selected patients. Patients requiring more pain relief may be treated with tramadol, 50 mg every 4-6 hours. Opioid analgesic combinations (eg, oxycodone, 5 mg, plus acetaminophen, 325 mg) may be administered every 6 hours as needed for severe pain.

► Coronary revascularization should be performed in selected persons with myocardial ischemia attributable to viable myocardium subserved by severely stenotic coronary arteries. Patients should be referred to a cardiologist if coronary revascularization is being considered.

Diuretics

Diuretics are the first-line drug in the treatment of elderly patients with HF and volume overload. A thiazide diuretic, such as hydrochlorothiazide, may be used to treat elderly patients with mild HF. A thiazide diuretic is ineffective, however, when the glomerular filtration rate is less than 30 ml/minute. 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.

Elderly patients with severe HF or concomitant renal insufficiency may need the addition of metolazone to the loop diuretic. Severe volume overload



Heart failure affects approximately 5 million U.S. adults. Here, the Fibonacci spiral is used as a metaphor to depict the myriad processes affecting, and those affected by, the aging heart, including hypertension, glomerular filtration, anemia, and ventricular rates.

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should be treated with intravenous diuretics and hospitalization.

Elderly patients with HF and a normal LVEF are especially sensitive to volume depletion. Because they require high LV filling pressures to maintain an adequate stroke volume and cardiac output, these elderly patients cannot tolerate intravascular depletion. Dehydration and prerenal azotemia

may occur if excessive doses of diuretics are given, making the standard of therapy the minimum effective dose of diuretics. Elderly patients with HF and an abnormal LVEF tolerate higher doses of diuretics than do elderly patients with HF and a normal LVEF. Therefore, older patients with HF and a normal LVEF should be treated with a low-sodium diet with cautious use rather

Table Treatment of elderly patients with heart failure and a normal left ventricular ejection fraction

- 1) Treat underlying and precipitating causes of heart failure
- 2) Treat hypertension, especially systolic hypertension, hyperlipidemia, myocardial ischemia, and anemia
- 3) Treat with cautious use of diuretics
- 4) Treat with beta blockers
- 5) Treat with angiotensin-converting enzyme (ACE) inhibitor
- 6) Treat with angiotensin II receptor blocker (ARB) if patient cannot tolerate ACE inhibitor because of cough, angioneurotic edema, rash, or altered taste sensation; move cautiously if angioneurotic edema with ACE inhibitor
- 7) Add isosorbide dinitrate plus hydralazine if heart failure persists
- 8) Add calcium channel blocker if heart failure persists
- 9) Avoid digoxin if sinus rhythm is present
- 10) Use exercise training as an adjunctive approach to improve clinical status in ambulatory patients

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than with large doses of diuretics. The dose of diuretics should be gradually reduced and stopped if possible when fluid retention is not present.

Beta blockers

Beta blockers should be used to treat elderly patients with HF and a normal LVEF unless there are contraindications to their use (see below). The goal is to slow the ventricular rate to less than 60 beats/minute. While the beneficial effects begin when the ventricular rate is reduced to less than 90, the benefits are optimal at a ventricular rate less than 60.

Beta blocker therapy increases LV diastolic filling time and, causing an increase in LV end-diastolic volume, reduces myocardial ischemia, decreases elevated blood pressure, decreases LV mass, and improves LV relaxation. 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.

Two prospective randomized studies have demonstrated that beta blockers reduce mortality in elderly patients with HF and a normal LVEF:

► In a prospective study, 158 patients (111 women and 47 men), mean age 81, with a prior MI, New York Heart Association (NYHA) class II or III HF, and a LVEF $\geq 40\%$ who were being treated with diuretics and angiotensin-converting enzyme (ACE) inhibitors for 2 months were randomized to propranolol or no propranolol.⁷ The initial dose of propranolol was 10 mg/d. This dose was increased by 10 mg increments at 10-day intervals until a dose of 30 mg 3 times daily was given. At 32-month follow-up, propranolol significantly reduced all-cause mortality by 35% and all-cause mortality plus nonfatal MI by 37%.⁷ Additionally, at 1-year follow-up, propranolol significantly increased LVEF from 57% to 63% and significantly decreased LV mass from 312 to 278 grams.⁷

► The SENIORS Study (Study of the Effects of Nebivolol Intervention on Outcomes and Rehospitalization in Seniors with Heart Failure) was a prospec-

tive, randomized, double-blind, placebo-controlled trial which investigated the effect of nebivolol in 2,128 patients, mean age 76, with HF (96% with NYHA class II or III HF) and an abnormal LVEF (65%) or a normal LVEF (35%) (these investigators diagnose an abnormal LVEF if it is less than 35%).⁸ ACE inhibitors or angiotensin receptor II blockers (ARBs) were administered to 89% of the patients. Coronary artery disease (CAD) was present in 68% of patients. CAD is a major cause of HF with a normal LVEF. At 21-month follow-up, the primary endpoint (all-cause mortality or cardiovascular hospital admission) was significantly reduced 14% by nebivolol.⁸ The primary endpoint was reduced by nebivolol by 14% in patients with an abnormal LVEF and by 17% in patients with a normal LVEF.⁸

Elderly patients with HF should 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.⁹ Beta blockers should be initiated in a low dose, such as carvedilol 3.125 mg/bid or metoprolol CR/XL 12.5 mg/d if there is NYHA class III or IV HF, or 25 mg/d if there is NYHA class II HF. The dose of beta blockers should be doubled at 2-3 week intervals, with the maintenance dose of beta blockers reached over 3 months (carvedilol 25 mg/bid or 50 mg/bid if over 187 pounds, or metoprolol CR/XL 200 mg/d). 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 indefinitely in this patient must be stressed because of their importance in reducing mortality.

During titration, the patient should be monitored for HF symptoms, fluid retention, hypotension, and bradycardia.⁹ If there is worsening of symptoms, increase the dose of diuretics or

ACE inhibitors. Temporarily lower the dose of beta blocker, if necessary.

CONTRAINDICATIONS to the use of beta blockers in patients with HF are bronchial asthma, severe bronchial disease, symptomatic bradycardia, symptomatic hypotension, and second-degree or third-degree atrioventricular block.

ACE inhibitors

Whereas data from large scale, prospective, randomized, placebo-controlled trials are needed to assess the efficacy of angiotensin-converting enzyme (ACE) inhibitors in treating elderly patients with HF and a normal LVEF, limited data does exist to support their use:

► At 3-month follow-up of 21 persons (mean age 80) with prior MI and HF with a normal LVEF treated with diuretics, patients randomized to enalapril had significant improvements in NYHA functional class, in treadmill exercise time, in LVEF, and in LV diastolic function assessed by Doppler echocardiography.¹⁰ Enalapril also significantly decreased cardiothoracic ratio measured from chest x-rays and echocardiographic LV mass.¹⁰

► In an observational study of 539 patients (55% women, mean age 75) with HF and a normal LVEF, ACE inhibitors decreased mortality and improved quality-of-life scores at 6-month follow-up.¹¹

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 over-diuresis before initiating treatment 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.

ARBs

An ARB (angiotensin II receptor blocker) should be used for treating HF with a normal LVEF if the patient can-

not tolerate an ACE inhibitor because of cough, angioneurotic edema, rash, or altered taste sensation and the benefits of a 5% reduction in hospitalization has been discussed with the patient.

► In the Candesartan in Heart failure: Assessment of Reduction in Mortality and morbidity (CHARM)—Preserved study, 3,023 patients (mean age 67; 27% age 75 and older) with HF and a normal LVEF were randomized to candesartan 32 mg/d or to placebo.¹² At 37-month follow-up, candesartan insignificantly reduced cardiovascular death or hospitalization for HF by 11%, but significantly reduced hospitalization for HF by 16%.¹²

Start ACE inhibitors in low doses after correction of hyponatremia or volume depletion

Isosorbide dinitrate plus hydralazine

If HF persists in elderly patients with a normal LVEF despite treatment with diuretics, beta blockers, and ACE inhibitors or ARBs, isosorbide dinitrate plus hydralazine should be added to the therapeutic regimen. In 83 nonelderly patients with HF and a normal LVEF in the Veterans Administration Cooperative Vasodilator-Heart Failure Trial I, compared with placebo, oral isosorbide dinitrate plus hydralazine insignificantly decreased mortality by 41%.¹³ (This study did not address the patient's race.)

Calcium channel blockers

Although calcium channel blockers should not be used to treat HF with an abnormal LVEF,¹ they may be added to

the therapeutic regimen if HF with a normal LVEF persists despite treatment with diuretics, beta blockers, ACE inhibitors or ARBs, and isosorbide dinitrate plus hydralazine. In a double-blind, 5-week crossover trial in 20 men with HF and a normal LVEF, compared with placebo, verapamil improved exercise capacity, peak LV filling rate, and a clinicoradiographic heart failure score.¹⁴ This small study is the only study that investigated the use of any calcium channel blocker in treating HF patients with a normal ejection fraction.

Digoxin

Digoxin should not be used to treat patients with HF in sinus rhythm with HF and a normal LVEF. 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 LVEF.¹⁵

► At 37-month follow-up of 988 patients, mean age 64, with HF and a LVEF >45% in the Digitalis Investigator Group (DIG) study, mortality was similar in patients treated with digoxin or placebo.^{16,17} Although HF hospitalization was insignificantly reduced 21% in patients with HF and a normal LVEF, all-cause hospitalization was insignificantly increased 4% in these patients.¹⁷ Hospitalization for suspected digoxin toxicity in patients treated with digoxin was:

- 0.67% in patients age 50-59,
- 1.91% in patients age 60-69,
- 2.47% in patients age 70-79, and
- 4.42% in patients age ≥80.¹⁷

A post-hoc subgroup analysis of data from all 1,926 women with HF and an abnormal or normal LVEF in the DIG study showed that digoxin significantly increased mortality by 20% in women.¹⁸ Based on these data, the author does not use digoxin to treat heart failure in women.

A retrospective analysis also showed in 988 men and women with HF and a

normal LVEF in the DIG study that higher NYHA classes were associated with poorer outcomes in patients with HF and a normal LVEF.¹⁹

Exercise training

Regular physical activity, such as walking daily as much as tolerated or using exercise bikes for as long as tolerated, should be encouraged in patients with mild to moderate HF and a normal LVEF to improve functional status and to decrease symptoms (Table 1). Patients with HF and a normal LVEF who are dyspneic at rest or at a low work level may benefit from a formal cardiac rehabilitation program.²⁰ A multidisciplinary approach to care is useful. A daily program of walking for as long as tolerated is useful for most elderly patients with HF. Segmental training, limb by limb, may offer the local benefits of walking on the peripheral circulation and skeletal muscles without stressing the heart. Patients can only be monitored in a formal cardiac rehabilitation program.

Coronary revascularization

Coronary revascularization is performed to improve prognosis, relieve symptoms, prevent ischemic complications, and improve functional capacity. The American college of Cardiology/American Heart Association guidelines recommend performing coronary angiography in patients with heart failure who have angina pectoris or significant stress-test induced myocardial ischemia unless the patient is not eligible for coronary revascularization.

Conclusion

Heart failure remains a major health problem in the United States. Given that the condition mainly affects the older patient, the incidence of HF will increase as our older patient population continues to grow over the coming decades.

This discussion has focused on the treatment of patients with HF and a normal LVEF, which represents the ma-

jority of patients with HF. To effectively manage this group as well as all patients with HF, the primary care physician needs to be familiar with the American College of Cardiology/American Heart Association guidelines. An understanding of the efficacy of appropriate drugs for HF, avoidance of drugs that may worsen the condition, and the role of exercise training in its management will help avert unplanned hospitalizations and reduce mortality in these vulnerable older patients. ©

Regular physical activity should be encouraged in patients with mild to moderate heart failure

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