in the clinic

Heart Failure

Section Editor
Barbara Turner, MD, MSED
Sankey Williams, MD
Darren Taichman, MD, PhD

Physician Writer
Lee R. Goldberg, MD, MPH

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CME Objective: To review current evidence for the prevention, diagnosis, and treatment of heart failure.

The information contained herein should never be used as a substitute for clinical judgment.

Annals of Internal Medicine

Approximately 5 million persons in the United States have heart failure, and according to the National Heart Lung and Blood Institute, the number is increasing. Heart failure is the most frequent cause of hospitalization in U.S. patients older than 65 years and leads to about 300 000 deaths per year (1). Heart failure is a major problem in the rest of the world as well, but few accurate data are available. The most common cause of heart failure in industrialized countries is ischemic cardiomyopathy, whereas other causes, such as infectious diseases, assume a larger role in underdeveloped countries. Despite recent advances in management of heart failure, the 30-day, 1-year, and 5-year mortality rates after hospitalization for heart failure are 10%, 22%, and 42%, respectively (2).

Prevention

What are the risk factors for heart failure?

Over the past decade, treatment of heart failure has shifted from focusing on acute exacerbations when the patient is "in" heart failure to treating heart failure as a chronic and potentially preventable syndrome. In the current model, there are risk factors that lead to heart failure, and modifying these risk factors can prevent symptoms and delay death. In addition, aggressive treatment can improve both the quantity and quality of life. The American College of Cardiology (ACC) and American Heart Association (AHA) have developed a staging system to help clinicians select therapies that improve outcomes for those at risk for or suffering from heart failure (3) (Box).

The incidence of heart failure approaches 10 per 1000 persons older than 65 years. At age 40 years, the lifetime risk for heart failure for both men and women is 1 in 5, and the same lifetime risk exists at age 80 years despite a much shorter life expectancy (1).

African Americans also face an increased risk for heart failure. African Americans between age 45 and 64 years are 2.5 times more likely to die of heart failure than white persons in the same age range (4). Men have a higher rate of heart failure than women, although this difference narrows as women get older.

Treat conditions and behaviors that are known to increase the risk for heart failure (Box). In addition, an epidemiologic study has linked increased risk for heart failure to physical inactivity, obesity, and lower levels of education (5).

Hypertension

Of persons presenting with heart failure, 75% have hypertension (1). Long-standing untreated hypertension is associated with both systolic and diastolic heart failure and is an independent risk factor for coronary artery disease (CAD). Clinical trials have shown that a reduction in systolic or diastolic blood pressure can reduce the risk for heart failure (6). Even modest decreases in systolic blood pressure reduce mortality and risk for heart failure (7).

Type 2 diabetes mellitus

Diabetes markedly increases the risk for heart failure and is an independent risk factor for CAD. In the population-based Reykjavik cross-sectional study of 19 381 participants, heart failure was diagnosed in 3.2% of all persons compared with 6.0% and 11.8% of persons with abnormal glucose regulation and type 2 diabetes, respectively (8).

The HOPE (Heart Outcomes Prevention Evaluation) trial found that, in patients at least 55 years old with either atherosclerosis

The ACC/AHA Guidelines for Stages of Heart Failure

Stage A: At risk for heart failure (coronary artery disease, hypertension, or diabetes mellitus) but has yet to show impaired left ventricular function or hypertrophy.

Stage B: Asymptomatic left ventricular dysfunction (has never had symptomatic heart failure).

Stage C: Current or past symptoms of heart failure associated with underlying structural heart disease.

Stage D: Has truly refractory heart failure and may be eligible for specialized, advanced treatment strategies, such as mechanical circulatory support, procedures to facilitate fluid removal, continuous inotropic infusions, or cardiac transplantation or other innovative or experimental surgical procedures, or for end-of-life care, such as hospice.

Common Conditions and Behaviors that Increase the Risk for Heart Failure

- Hypertension
- Diabetes
- Cardiotoxic substance use
- Hyperlipidemia
- Thyroid disorders
- Tachycardia
- Coronary artery disease

or diabetes and at least 1 other risk factor but no history of heart failure, the angiotensin-converting enzyme (ACE) inhibitor ramipril reduced the risk for stroke, myocardial infarction (MI), and death from cardiovascular disease by 22% while also significantly reducing heart failure (7).

Cardiotoxic substance use

Alcohol is a direct myocardial toxin and can be the primary cause of heart failure. Abstinence from alcohol may reverse left ventricular dysfunction (9). Despite the lack of clinical trials, most clinicians recommend abstinence from alcohol or limited alcohol intake for patients with left ventricular dysfunction. Tobacco and cocaine use significantly increase the risk for CAD, which can lead to heart failure. Cocaine also has direct effects on the myocardium. Chemotherapeutic agents, such as anthracycline and trastuzumab, can also exert toxic effects on the myocardium.

Hyperlipidemia

Hyperlipidemia is strongly associated with CAD, which may lead to heart failure. Large-scale clinical trials have shown the benefit of lipid lowering for primary and secondary prevention of cardiovascular events.

The CARE (Cholesterol and Recurrent Events) trial found that pravastatin significantly reduced the incidence of heart failure, subsequent cardiovascular events, and mortality (10).

Thyroid disorders

Both hyperthyroidism and hypothyroidism are associated with heart failure, and restoration of a euthyroid state can potentially return ventricular function to normal (11, 12). Hyperthyroidism is associated with atrial fibrillation and tachycardia, which may complicate or worsen heart failure.

Tachycardia

Studies have shown that rapid prolonged ventricular rates can lead to cardiomyopathy. Restoration of normal rhythm or rate control in patients with poorly controlled atrial fibrillation and other supraventricular tachycardias can improve function and potentially prevent left ventricular dysfunction (13-15).

Coronary artery disease

Because coronary disease is a major risk factor for heart failure, aggressive risk-factor modification with cholesterol-lowering drugs and aspirin, ACE inhibitors, and β-blockers can significantly reduce mortality and the risk for future cardiovascular complications, including heart failure. Although hypertension is the most common risk factor for heart failure, antecedent MI is a very close second (16).

The CAPRICORN (Carvedilol Post-Infarct Survival Control in Left Ventricular Dysfunction) trial showed that the β-blocker carvedilol significantly reduced mortality in patients with left ventricular dysfunction with or without heart failure after MI and who also received ACE inhibitors, revascularization, and aspirin (17).

What medications should be used for primary prevention of heart failure?

Several classes of medications have been shown to prevent heart failure in at-risk populations. These include hydroxymethylglutaryl coenzyme A reductase inhibitors in patients with hyperlipidemia, ACE inhibitors in patients with diabetes, and nearly all antihypertensive medications when used to lower blood pressure to goal levels.

What nondrug interventions should be used for primary prevention of heart failure?

There is increasing evidence that obesity and decreased physical activity can increase the risk for heart failure (5). Maintaining a healthy weight and exercising regularly can help lower blood pressure and lipids, both of which reduce the risk for coronary disease. Obstructive sleep apnea is also associated with hypertension and a much higher incidence of heart failure and cardiovascular disease in general (18). Treatment of

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sleep apnea may reduce this risk (19, 20). Smoking cessation can significantly reduce the risk for cardiovascular disease, including heart failure (21). There is no evidence that the routine use of nutritional supplements can prevent left ventricular dysfunction.

Prevention... Risk factors for heart failure include hypertension; diabetes; the use of cardiotoxic substances, such as alcohol, tobacco, and cocaine; hyperlipidemia; thyroid disorders; tachycardia; and coronary artery disease. Treatment for these risk factors reduces the risk for heart failure.

CLINICAL BOTTOM LINE

Diagnosis

What symptoms and signs should prompt clinicians to consider the diagnosis of heart failure?

Patients with underlying risk factors, including CAD, valvular heart disease, and long-standing hypertension may be asymptomatic. Do not wait for symptoms to develop before evaluating and treating these patients for early left ventricular dysfunction (Stage B). There is very strong evidence that treatment of asymptomatic left ventricular dysfunction will delay the onset of symptomatic heart failure and improve survival (22).

Once structural or functional heart disease affects the ability of the myocardium to fill and pump blood normally, patients may develop dyspnea, fatigue, exercise intolerance, and fluid retention that leads to pulmonary congestion and edema. The breathing difficulties and cough of heart failure are sometimes initially misdiagnosed as bronchitis, pneumonia, or asthma, especially in young patients. Physical signs of heart failure may reflect the underlying cause, as shown by elevated blood pressure or an abnormal cardiac murmur, or the resulting fluid retention, as shown by elevated jugular venous pressure, pulmonary crackles, a third heart sound, and lower-extremity edema.

What are the types of heart failure, and how should clinicians distinguish them?

Heart failure has many causes, and it is sometimes useful to divide them into dilated, hypertrophic, and restrictive types. Most causes of heart failure lead to cardiac dilatation. Hypertrophic cardiomyopathy is due to genetic abnormalities or hypertension. Restrictive heart failure is usually due to systemic infiltrative diseases.

More important is the functional distinction between systolic heart failure and heart failure with preserved left ventricular function. In systolic heart failure, the heart is dilated, and the ejection fraction is below 50%. In heart failure with preserved left ventricular function, which occurs more often in elderly patients with hypertension, there is less dilatation and a normal ejection fraction. In patients with heart failure, those with preserved ejection fraction are responsible for 50% of hospitalizations and have a similar survival rate as those with systolic heart failure (23, 24).

What is the role of B-type natriuretic peptide in the evaluation and treatment of heart failure?

Serum levels of B-type natriuretic peptide (BNP) and N-terminal-pro-B-type natriuretic peptide (NTproBNP) increase with increases in ventricular volume and pressure (25) and therefore can be used as markers for ventricular volume and pressure overload. NT-proBNP has a longer half-life in the serum than does BNP. The best data for the usefulness of both BNP and NTproBNP are in the setting of acute dyspnea to determine the contribution of heart failure, especially with concomitant

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pulmonary disease (26). BNP levels also can be elevated in women, older patients, persons with renal disease, obese patients, and in patients with acute MI and some noncardiac conditions, so interpret them in the context of all available clinical data and do not consider them as stand-alone tests (27).

In addition, BNP levels can be helpful in risk stratification and prognosis (28). Routine monitoring of BNP and NTproBNP remains controversial, and studies to resolve the controversy are underway (29).

What other tests should clinicians consider in the evaluation of patients with suspected heart failure?

Electrocardiography

The ACC and AHA recommend electrocardiography (ECG) in any patient at risk for or with a history of cardiac disease, including new-onset or exacerbated heart failure. Whenever possible, compare the tracing with a previous baseline tracing. Results can show the presence of ventricular hypertrophy, atrial abnormality, arrhythmias, conduction abnormalities, previous MI, and active ischemia.

Echocardiography

Perform 2-dimensional echocardiography with Doppler in all patients with suspected heart failure. It is a key study for determining left ventricular cavity size and function, identifying wall motion abnormalities, measuring left ventricular ejection fraction (LVEF) and right ventricular function, documenting the presence of valvular abnormalities, and differentiating between systolic heart failure and heart failure in the setting of preserved left ventricular function. In heart failure with preserved left ventricular function, the ejection fraction is normal (>50%), and there is evidence of ventricular hypertrophy. In systolic dysfunction, the ejection fraction is less than 50%, and left ventricular dilatation is often present. The degrees of left ventricular systolic and diastolic dysfunction are important in predicting prognosis, and the treatment of systolic heart failure may differ from the treatment of heart failure with preserved left ventricular function.

Stress testing

Use a traditional exercise stress test to evaluate patients for coronary ischemia, to quantify functional capacity, and to identify exercise-induced arrhythmias. Use pharmacologic stress testing with dipyridamole, dobutamine, or adenosine with nuclear imaging or echocardiography to look for ischemia in patients who cannot exercise. Use metabolic stress testing with respiratory gas analysis to determine the extent of disability, to differentiate between cardiac or pulmonary limitation to exercise, and to determine functional class in patients who are candidates for cardiac transplantation or in whom the cause of exercise intolerance is unclear (30).

Cardiac catheterization and endomyocardial biopsy

Consider cardiac catheterization in patients with heart failure when echocardiography is insufficient to define the severity of valvular heart disease and when ischemic heart disease is present or suspected. In addition, do a right heart catheterization in patients who do not respond to traditional therapies or in whom pulmonary hypertension may be contributing to their symptoms. Do not perform an endomyocardial biopsy in most patients with suspected myocarditis unless giant-cell myocarditis is being considered.

Other laboratory studies

To rule out occult thyroid disease, consider obtaining serum levels of thyroid-stimulating hormone in all patients with new-onset heart failure. Because anemia, renal insufficiency, infection, and concurrent pulmonary disease can exacerbate

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heart failure, consider including a complete leukocyte count, serum electrolytes, blood urea nitrogen, serum creatinine, chest radiography, pulmonary function studies, and appropriate cultures.

Diagnosis... Be alert for the development of heart failure in any patient with vascular disease; older persons; African Americans; men; patients with hypertension, hyperlipidemia, and diabetes; and patients who smoke, drink alcohol, or use illicit drugs. Dyspnea and fatigue are the primary symptoms of heart failure. In addition to history and physical examination, use 2-dimensional Doppler echocardiography to assess left ventricular function along with ECG and additional studies to determine the cause of the heart failure and to identify exacerbating factors.

CLINICAL BOTTOM LINE

Treatment

How should clinicians evaluate functional capacity in patients with suspected heart failure to determine treatment?

Clinicians should determine functional capacity by using the New York Heart Association (NYHA) classification system (Box). Tracking changes in clinical NYHA class at every visit may identify patients with progressive heart failure who may eventually benefit from specialized care or cardiac transplantation.

Additional functional capacity tests that can be followed over time include the 6-minute walk test (Box) and formal exercise or pharmacologic stress testing. Measuring peak oxygen consumption ($\dot{V}0_2$) at the time of exercise testing is the most potent predictor of prognosis, but the testing is not available at all centers.

What are the key points of the updated heart failure guidelines?

The ACC/AHA guidelines for the diagnosis and management of heart failure in adults were updated in 2009. Several key changes were made to reflect new information from clinical trials from North America and around the world. The one new section is on the hospitalized patient with acute heart failure. This section emphasizes the importance of identifying the cause of the decompensation, including acute coronary syndromes and coronary ischemia, severe hypertension, atrial and ventricular arrhythmias, infections, pulmonary emboli, renal failure, and medical or dietary nonadherence. In addition, the guidelines emphasize early use of loop diuretics to relieve volume overload and frequent assessments for hypoperfusion and end-organ dysfunction. Finally, there are recommendations regarding important processes, including medication reconciliation, patient and family education, initiation of guideline-mandated medications, and early postdischarge follow-up.

The updated guidelines also include strengthened recommendations on 2 medications, hydralazine and isosorbide dinitrate, that are particularly effective in African Americans when combined with ACE inhibitors and β-blockers. In addition, the guidelines have been updated to reflect new information on the use of implantable cardioverter-defibrillators (ICDs) and cardiac resynchronization (CRT) devices. The guidelines urge clinicians to consider the functional capacity and overall prognosis of the patient before recommending an ICD. The guidelines support the use of CRT to improve symptoms, exercise capacity, quality of life, LVEF, and survival and to decrease hospitalizations in patients with persistently symptomatic

New York Heart Association (NYHA) Classification System

- NYHA class I (mild): Patient has asymptomatic left ventricular dysfunction. Normal physical activity does not cause undue fatigue, palpitation, or shortness of breath.
- NYHA class II (mild): Patient has fatigue, palpitation, or shortness of breath with normal physical activity.
- NYHA class III (moderate): Patient has shortness of breath with minimal activity, including usual activities of daily living.
- NYHA class IV (severe): Patient has shortness of breath at rest and is unable to perform any physical activity without discomfort. Physical activity of any kind increases discomfort.

How to Perform the 6-Minute Walk Test

Ask the patient to walk for 6 minutes in a straight line back and forth between 2 points separated by 60 feet. Allow the patient to stop and rest or even sit, if necessary. At either end of the course, place chairs that can quickly be moved if the patient needs to sit. Note the total distance walked in 6 minutes, which correlates well with other measures of functional capacity. Sex-specific equations have been developed that use age, height, and weight to calculate predicted distances for healthy adults.

heart failure who are undergoing optimum medical therapy and have cardiac dyssynchrony (as evidenced by a prolonged QRS duration).

Finally, the guidelines clarify the treatment goals in patients with both heart failure and atrial fibrillation. The primary goals are ventricular rate control using β-blockers and anticoagulation using warfarin.

When should clinicians begin first-line drug therapy with ACE inhibitors or angiotensin-receptor blockers? What are the alternatives for patients who cannot tolerate these drugs?

ACE inhibitors

Use ACE inhibitors in all patients with left ventricular dysfunction regardless of functional class (even in the absence of symptoms) except in patients with intolerance or a contraindication, such as angioedema. These vasodilators alter the natural history of the disease and improve survival and quality of life. Numerous randomized, placebo-controlled clinical trials have shown that ACE inhibitors reduce mortality in patients with left ventricular dysfunction, even in those without symptoms.

CONSENSUS (Cooperative North Scandinavian Enalapril Survival Study) evaluated 253 patients with NYHA class I to IV heart failure who were randomly assigned to enalapril or placebo in a blind study. All patients were also receiving diuretics, and 93% received digitalis glycosides. The mortality rate was reduced by 27% (P < 0.001) in the patients receiving enalapril compared with placebo (31).

The SOLVD (Studies of Left Ventricular Dysfunction) treatment trial randomly assigned 2569 patients with NYHA class I to IV heart failure to enalapril or placebo. In patients with heart failure, those receiving enalapril had a 16% (P < 0.005) reduction in mortality rate, a 30% (P < 0.001) reduction in heart failure hospitalizations, a 7% (P < 0.01) reduction in total hospitalizations, a 44% (P < 0.01) reduction in worsening heart failure, and a 23% (P < 0.02) reduction in MI (32) compared with those receiving placebo.

The SOLVD prevention trial enrolled 4228 patients with NYHA class I heart failure and asymptomatic left ventricular dysfunction and randomly assigned them to enalapril or placebo. Patients receiving enalapril had an 8% reduction in mortality rate, a 31% (P < 0.001) reduction in heart failure hospitalizations, a 50% (P < 0.01) reduction in episodes of worsening heart failure, and a 24% (P < 0.01) reduction in MI compared with those receiving placebo (33).

Initiate enalapril, captopril, lisinopril, or ramipril at low doses and titrate upward while monitoring blood pressure. The end point for blood pressure can be as low as 80 to 90 mm Hg systolic blood pressure as long as the patient is asymptomatic. Important side effects include cough, worsening renal insufficiency, and hyperkalemia.

Angiotensin-receptor blockers

Consider using angiotensin-receptor blockers (ARBs) in patients who have intolerable side effects from ACE inhibitors, such as cough.

The ELITE (Evaluation of Losartan in the Elderly) I trial compared captopril with losartan in elderly patients with heart failure and showed a decrease in all-cause mortality (8.7% vs 4.8%; risk reduction, 46%; P = 0.035) in the losartan group. Admissions with heart failure were the same in both groups (5.7%), as was improvement in NYHA functional class from baseline (34). *The ELITE II trial also compared captopril with losartan, but all-cause mortality (11.7% vs. 10.4% average annual mortality rate), sudden death, and resuscitated arrests (9.0% vs. 7.3%) did not significantly differ between the groups (hazard ratios, 1.13 [95% CI, 0.95 to 1.35]; P = 0.16, and 1.25 [CI, 0.98 to 1.60]; P = 0.08)* (35).

Val-HeFT (Valsartan-Heart Failure Trial) randomly assigned patients with heart failure to valsartan or placebo in addition to standard heart failure medications. Mortality did not differ between groups, but the incidence of the combined end point of morbidity or mortality was 13.2% lower with valsartan than with placebo (relative risk, 0.87 [CI, 0.77 to 0.97]; P = 0.009) (36). In a subgroup analysis, patients who were not receiving an ACE inhibitor but who were randomly assigned to receive valsartan had a 33% reduction

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in all-cause mortality. This result is similar to the magnitude of mortality reduction with ACE inhibitors (37).

Evidence from the randomized, placebo-controlled CHARM (Candesartan Cilexitil [Atacand] in Heart Failure Assessment of Reduction in Mortality and Morbidity)-Alternative trial showed that the ARB candesartan decreased a combined end point of death from cardiovascular causes or hospitalization due to heart failure when compared with placebo in patients with left ventricular dysfunction who could not tolerate ACE inhibitors (38).

Some studies have suggested that combining ACE inhibitors and ARBs may be beneficial in reducing left ventricular size and decreasing hospitalizations with an equivocal effect on mortality (34-38). Patients should be carefully monitored for hyperkalemia and renal dysfunction. For patients with elevated blood pressure despite maximum ACE inhibitor and β-blocker dosing, consider the addition of an ARB in non-African Americans or the combination of hydralazine and long-acting nitrates in African Americans.

Hydralazine and nitrates

Patients who cannot tolerate either ACE inhibitors or ARBs should receive hydralazine and long-acting nitrates. This combination improves clinical outcomes and decreases mortality in patients with heart failure and depressed ejection fraction (39, 40). However, the combination does not seem to have as much effect on mortality rates as ACE inhibitors. Hydralazine plus nitrates should also be considered in addition to standard therapy, including an ACE inhibitor or ARB, in African-American patients with symptomatic heart failure, because this combination may favorably affect myocardial remodeling and mortality in these patients.

A-HeFT (African American Heart Failure Trial), which compared isosorbide plus hydralazine with placebo in African Americans with heart failure, showed that adding this therapy increased survival in those who were already taking other neurohormonal blockers, including ACE inhibitors and β-blockers (41).

When should clinicians add β-blockers, aldosterone antagonists, and loop diuretics?

β-Blockers

β-Blockers should be used in all NYHA classes of heart failure if the patient is stable on ACE inhibitors or other vasodilators and is not volume overloaded. β-Blockers can reduce heart failure symptoms, improve clinical outcomes and ejection fraction, and significantly decrease mortality rate. Patients with less severe heart failure have the greatest long-term benefit, including those with left ventricular dysfunction but no symptoms. Many studies testing carvedilol, bisoprolol, and long-acting metoprolol succinate have found reductions in hospitalizations, sudden death, and overall mortality in patients with heart failure. Data on other β-blockers are lacking; therefore, clinicians should select one of the agents for which mortality data are available.

The CAPRICORN trial randomly assigned patients with left ventricular dysfunction after MI with or without heart failure to β-blockade with carvedilol. There was a significant reduction in mortality that was even more marked in the group without symptomatic heart failure (17).

The U.S. carvedilol trial randomly assigned 696 patients to the carvedilol group and 398 to the placebo group. Patients were classified with NYHA class I to IV heart failure. A 65% ($P < 0.001$) reduction in mortality was seen in the carvedilol group. Cardiovascular hospitalizations were reduced (42).

The CIBIS (Cardiac Insufficiency Bisoprolol Study) I randomly assigned 320 patients to bisoprolol, 5 mg/d, or placebo. There was a statistically insignificant 20% reduction in mortality and a significant reduction in heart failure hospitalizations (43). The CIBIS II randomly assigned patients with NYHA class III to IV heart failure to bisoprolol, 5 mg/d, or placebo. A total of 3.6% of patients in the bisoprolol group had sudden cardiac death versus 6.3% in the placebo group ($P < 0.01$) (44).

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The MERIT-HF (Metoprolol CR/XL Randomized Intervention Trial-Heart Failure) randomly assigned 3991 patients with NYHA class II to IV heart failure to metoprolol CR/XL, up to 200 mg/d, versus placebo. All-cause mortality was reduced 34% (P < 0.001), and sudden death was reduced 59% (P < 0.001) for patients receiving metoprolol versus placebo (45).

The COPERNICUS (Carvedilol Prospective Randomized Cumulative Survival) trial randomly assigned patients with NYHA class IV heart failure to carvedilol or placebo. The combined risk for death or hospitalization decreased 24% with carvedilol (P < 0.001) (46).

Initiate β-blockers at the lowest dose and slowly titrate upward every 2 to 4 weeks to the highest therapeutic dose tolerated, as limited by bradycardia, hypotension, or side effects. Instruct patients to check their body weight and watch for worsening heart failure symptoms during initiation and upward titration of β-blockade.

Aldosterone antagonists

If patients continue to have NYHA class III to IV symptoms despite therapy with ACE inhibitors and β-blockers, consider treatment with low doses of an aldosterone antagonist. Spironolactone has been studied the most but can occasionally cause painful gynecomastia in men.

RALES (Randomized Aldosterone Evaluation Study), a large, randomized, placebo-controlled trial involving 1663 patients with NYHA class III to IV heart failure on appropriate therapy with or without spironolactone, was halted 18 months early by the Data Safety Monitoring Board because there were significantly fewer deaths in the spironolactone group than in the placebo group (284 vs. 386 deaths; 35% reduction; P < 0.001) (47).

Eplerenone is a newer, more selective aldosterone antagonist with fewer undesirable side effects and has been shown to decrease all-cause mortality in patients with an ejection fraction less than 40% after acute MI (48).

Higher rates of hyperkalemia have been found in patients taking ACE inhibitors and spironolactone, necessitating careful monitoring of serum potassium levels (49). Weekly serum electrolytes should be obtained until there is evidence of stability in potassium levels. The combination of ACE inhibitors, ARBs, and spironolactone should be avoided because of a significantly increased risk for hyperkalemia.

Diuretics

Diuretics, which are the only therapy that acutely produces symptomatic benefits, can reduce pulmonary capillary wedge pressure and edema and improve exercise capacity. No clinical trials have assessed their long-term safety or effect on mortality in heart failure.

A single trial comparing furosemide with torsemide found that torsemide had better oral absorption and that patients receiving torsemide were less likely to be readmitted for heart failure (50).

In general, torsemide or bumetanide should be reserved for patients who do not respond to adequate doses of furosemide.

Loop diuretics should be used in combination with a low-sodium diet to control volume overload, maintain a stable weight, and improve the functional capacity of patients with NYHA class II to IV heart failure. Diuretics should never be used alone to treat heart failure, because they do not prevent the progression of disease or maintain clinical stability over time.

For patients resistant to loop diuretics, thiazide diuretics may be added to augment diuresis. Furthermore, the use of a thiazide diuretic in combination with a loop diuretic can be part of an effective "sliding" diuretic regimen based on a patient's daily weight and symptoms. A second class of diuretic may act synergistically with the first by blocking the adaptive processes that limit diuretic

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effectiveness. With all diuretics, clinicians should frequently monitor patient renal function and electrolytes, especially potassium levels.

What is the role of digoxin in the treatment of heart failure?

Digoxin can alleviate symptoms and decrease hospitalizations in patients with heart failure; however, it should be reserved specifically for patients with symptomatic NYHA class II to IV heart failure, because research indicates that it provides no survival difference compared with placebo (51). Furthermore, digoxin alone does not seem to be effective in rate control for patients with atrial fibrillation, because it provides only rate control at rest (52). The ACC/AHA guidelines recommend the use of a β-blocker with digoxin for rate control of atrial fibrillation.

Ensure that electrolytes and renal function are stable before starting digoxin, and monitor serum levels, especially if renal function is changing. Some controversy exists over the appropriate serum level of digoxin. A recent study suggested that lower serum levels of digoxin were as efficacious as "therapeutic" levels, with a lower risk for side effects (53). In fact, in a post hoc subgroup analysis of 1 recent study, mortality rate was increased in women receiving digoxin compared with men, which may have been due to higher serum digoxin levels (54).

What drug therapy is appropriate for patients with heart failure and preserved left ventricular function?

The goals of heart failure treatment in the setting of preserved left ventricular function are to control heart rate to allow for adequate filling of the ventricle; to maintain normal sinus rhythm, if possible; to control volume status to decrease diastolic pressures; to control blood pressure or other stimuli predisposing to left ventricular hypertrophy; and to minimize myocardial ischemia in the setting of left ventricular hypertrophy, even in the absence of epicardial coronary disease.

There have been few randomized trials of the treatment of heart failure with preserved left ventricular function, and recommendations are based on investigations in small groups of patients or on theoretical concepts. The publication of consensus guidelines on the definition of heart failure with preserved left ventricular function has allowed for the design of multicenter clinical trials (55).

ACC/AHA and other guidelines suggest that patients with heart failure with preserved left ventricular function should be treated with diuretics, β-blockers, ACE inhibitors, ARBs, and nitrates. Calcium-channel blockers, such as verapamil and diltiazem, may also alleviate symptoms and improve exercise capacity. Avoid overdiuresis, because dehydration can lead to lightheadedness and syncope in patients with diastolic dysfunction.

When should clinicians use inotropic agents in patients with heart failure?

Inotropic agents, such as dobutamine and milrinone, can improve cardiac output in patients with low cardiac output and decrease afterload in patients with severe heart failure unresponsive to the traditional heart failure medications. However, all inotropic agents, except digoxin, have been associated with excess mortality and should be reserved for patients unresponsive to traditional oral medications for heart failure. Inotropic agents can be used short-term to stabilize cardiogenic shock and to allow for other therapies, including revascularization, valve repair, or initiation of more traditional therapies. In addition, inotropic agents can be used to bridge a patient to cardiac transplantation or insertion of a left ventricular assist device. Finally, inotropic agents can be used as palliation when heart failure becomes refractory and the patient is not a candidate for

48. Eplerenone Post-Acute Myocardial Infarction Heart Failure Efficacy and Survival Study Investigators. Eplerenone, a selective aldosterone blocker, in patients with left ventricular dysfunction after myocardial infarction. N Engl J Med. 2003;348:1309-21. [PMID: 12668699]
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either cardiac transplantation or a ventricular assist device.

When should clinicians consider using anticoagulants in patients with heart failure?

Embolic stroke is associated with dilated cardiomyopathy with depressed ejection fraction below 35%, valvular lesions (especially mitral stenosis), and atrial fibrillation. The incidence of thromboembolic events was about 2.7 per 100 patient-years in 1 large trial of patients with heart failure (56). Many experts advocate anticoagulation to reduce the risk for stroke in patients with heart failure and depressed ejection fraction below 35% who have no contraindications, but anticoagulation remains controversial for such patients without atrial fibrillation, documented clot, or valvular heart disease. In 1 trial, the use of warfarin in such patients was not associated with a reduction in all-cause mortality (57). Therefore, it seems most appropriate to initiate anticoagulation with warfarin in patients with left ventricular clot documented on echocardiogram or ventriculogram, atrial fibrillation, or previous embolic event and to use aspirin or clopidogrel in patients with coronary disease regardless of ejection fraction.

What should clinicians advise patients about exercise? Do formal exercise programs provide benefit?

Exercise improves physical and psychological well-being. In patients with heart failure, it improves peak $\dot{V}O_2$ (58, 59) as well as metabolic and hemodynamic indices and delays the onset of the anaerobic threshold (58, 60). A recent National Institutes of Health–sponsored clinical trial found that 30 minutes of exercise on a treadmill or stationary bicycle most days of the week led to a significant reduction in death or heart failure complications (61).

Enroll patients with medically stable NYHA class II, III, and perhaps class IV heart failure in a long-term aerobic exercise program tailored to the patient's functional capacity. A structured cardiac rehabilitation program may be particularly effective, because it can provide supervised exercise as well as support in making lifestyle modifications. Patients with worsening heart failure should temporarily stop exercise until symptoms are stabilized. In addition, if patients show evidence of exercise-induced ischemia, stop exercise until further evaluation and therapy are initiated.

When should clinicians consider placement of an intracardiac device in patients with heart failure?

Consider placement of an ICD to monitor heart rate and rhythm and to correct arrhythmia when it occurs for patients with left ventricular dysfunction and an ejection fraction less than 30% in NYHA class I, II, or III and an overall life expectancy of more than 6 months. Data suggest that patients with class IV symptoms do not benefit from ICDs and that patients with class II symptoms may benefit most (1, 62, 63). Studies show a clear decrease in sudden death and overall mortality. Consider the patient's functional capacity as well as overall prognosis before recommending an ICD.

The DEFINITE (Defibrillators in Non-ischemic Cardiomyopathy Treatment Evaluation) trial randomly assigned 458 patients with dilated nonischemic cardiomyopathy and LVEF less than 36% to standard medical therapy or standard medical therapy plus a single-chamber ICD. Over 29 months of follow-up, 28 deaths occurred in the ICD group compared with 40 in the standard medical therapy group. Although overall mortality was not significantly lower, there were 3 sudden deaths in the ICD group versus 14 in the standard therapy group (P = 0.006) (64).

In MADIT (Multicenter Automatic Defibrillator Implantation Trial) II, 1232 patients with a previous MI and an ejection fraction less than 30% were randomly assigned (in the absence of electrophysiologic testing or other risk stratification) to ICD

56. Dunkman WB, Johnson GR, Carson PE, et al. Incidence of thromboembolic events in congestive heart failure. The V-HeFT VA Cooperative Studies Group. Circulation. 1993;87:VI94-101. [PMID: 8500246]
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63. Bardy GH, Lee KL, Mark DB, et al. Amiodarone or an implantable cardioverter-defibrillator for congestive heart failure. N Engl J Med. 2005;352:225-37. [PMID: 15659722]

placement with conventional drug therapy or conventional drug therapy alone. The ICD group had a 28% reduction in mortality at 3 years (P = 0.007) (62).

SCD-HeFT (Sudden Cardiac Death in Heart Failure Trial) randomly assigned 2521 patients with NYHA class II or III heart failure and an LVEF less than 35% to conventional therapy for heart failure plus placebo; conventional therapy plus amiodarone; or conventional therapy plus a conservatively programmed, shock-only, single-lead ICD. During a median follow-up of 45.5 months, mortality was 29% in the placebo group, 28% in the amiodarone group, and 22% in the ICD group. The ICD therapy was associated with a 23% decreased risk for death (P = 0.007) compared with placebo (63).

Placement of a biventricular pacemaker can improve quality of life and decrease hospitalizations in patients with heart failure, an ejection fraction less than 35%, a QRS interval greater than 120 msec on ECG, and symptoms despite maximum medical therapy. In addition, those with NYHA class I and II heart failure may benefit from decreased hospitalizations and improved ejection fractions.

In the MIRACLE-ICD (Multicenter InSync ICD Randomized Clinical Evaluation) trial, 369 patients with class III or IV heart failure, ejection fraction, and a QRS interval of 130 msec or more received an ICD with resynchronization device. Those in whom the device was turned on had improved quality of life, functional status, and exercise capacity but no change in heart failure status, rates of hospitalization, or survival (65).

In the CARE-HF (Cardiac Resynchronization in Heart Failure) study, 813 patients with NYHA class III or IV heart failure due to left ventricular systolic dysfunction and cardiac dyssynchrony who were receiving standardized drug therapy were randomly assigned to receive medical therapy alone or with cardiac resynchronization. The study concluded that, in these patients, cardiac resynchronization improved symptoms and quality of life and reduced the risk for death (66).

In MADIT-CRT, 1820 patients with ischemic or nonischemic cardiomyopathy, an ejection fraction of 30% or less, a QRS duration of 130 msec or more, and NYHA class I or II symptoms were randomly assigned to CRT-ICD or ICD alone. There was a 41% reduction in the risk for heart failure in the CRT-ICD group, a finding that was evident primarily in a prespecified subgroup of patients with a QRS duration of 150 msec or more. CRT was associated with a significant reduction in left ventricular volumes and improvement in the ejection fraction. The overall risk for death did not significantly differ between the 2 groups, with a 3% annual mortality rate in each treatment group (67).

When should clinicians hospitalize patients with heart failure?

Hospitalize patients with severe NYHA class IV heart failure, characterized by dyspnea at rest, severe fatigue, or volume overload unresponsive to oral diuretics. Also hospitalize patients with life-threatening ventricular arrhythmias, atrial arrhythmias that worsen heart failure symptoms or cause hypotension, syncope, or sudden cardiac death. Finally, hospitalize patients with heart failure and unstable angina or new ECG changes to rule out MI.

When should clinicians consult a cardiologist about management of patients with heart failure?

If symptoms worsen despite optimum medical therapy, consult a cardiologist about the need for hospitalization for parenteral inotropic drug treatment; catheterization; placement of an ICD, biventricular pacemaker, or left ventricular assist device; or cardiac transplantation. Any signs or symptoms of new or worsening coronary ischemia should also prompt cardiology consultation. In addition, patients with any of the ominous signs of advanced heart failure, including intolerance to any afterload-reducing agent or β-blocker, hyponatremia, worsening renal function, or frequent hospitalizations, may benefit from evaluation by a cardiologist. Consider obtaining pulmonary consultation when primary lung disease, such as chronic obstructive pulmonary disease or sleep apnea,

64. Kadish A, Dyer A, Daubert JP, et al. Prophylactic defibrillator implantation in patients with nonischemic dilated cardiomyopathy. N Engl J Med. 2004;350:2151-8. [PMID: 15152060]
65. Young JB, Abraham WT, Smith AL, et al. Combined cardiac resynchronization and implantable cardioversion defibrillation in advanced chronic heart failure: the MIRACLE ICD Trial. Multicenter InSync ICD Randomized Clinical Evaluation (MIRACLE ICD) Trial Investigators. JAMA. 2003;289:2685-94. [PMID: 12771115]
66. Cleland JG, Daubert JC, Erdmann E, et al. The effect of cardiac resynchronization on morbidity and mortality in heart failure. N Engl J Med. 2005;352:1539-49. [PMID: 15753115]
67. Moss AJ, Hall WJ, Cannom DS, et al. Cardiac-resynchronization therapy for the prevention of heart-failure events. N Engl J Med 2009;361:1329-1338. [PMID: 19723701]

is believed to be contributing to the patient's symptoms.

What is the role of diet and monitoring weight in the management of heart failure?

Despite a lack of definitive evidence, ACC/AHA and other guidelines recommend sodium restriction in patients with symptomatic heart failure and the avoidance of salt-retaining medications, such as nonsteroidal anti-inflammatory drugs. Some clinicians recommend that patients with more advanced heart failure limit intake to 2 g of sodium per day and 2 qt of fluid per day to increase the effectiveness of diuretic therapy. Limitation of salt and fluid intake results in fewer hospitalizations for decompensated heart failure. Patients who have cardiovascular risk factors, such as hyper-lipidemia, obesity, or diabetes, should also be encouraged to follow dietary recommendations specific to these underlying conditions.

Monitoring daily weight can prevent heart failure exacerbations by allowing for adjustments in diuretics. Instruct patients to weigh themselves daily and contact their clinician for instructions on how to adjust their diuretics if their weight exceeds a predetermined threshold (usually 2-lb increase overnight or 5-lb increase over 3 days).

What other approaches should clinicians recommend to patients to prevent exacerbations of heart failure?

Advise patients to adhere to their fluid and salt restriction and medical regimen, to weigh themselves daily, and to report deviations from their "dry weight" before they become symptomatic. Some patients can learn to use a sliding dose of diuretic to maintain their weight. Support from nurses, dietitians, home health staff, and physical therapists can be invaluable in helping patients prevent exacerbations. Patients should receive pneumococcal vaccine and annual influenza immunization.

Patients with established CAD should begin aggressive risk-factor modification, including attention to diet, exercise, weight control, and smoking cessation. Prescribe behavior modifications and pharmacologic therapy unless contraindicated. Many studies have shown that risk-factor modification with cholesterol-lowering drugs and the use of aspirin or other antiplatelet drugs, ACE inhibitors, and β-blockers can significantly reduce the risk for future cardiovascular events and can reduce mortality.

Treatment... Determine NYHA functional class to guide treatment in patients with heart failure. Limit salt and fluid intake in patients with symptomatic heart failure, and recommend regular exercise as tolerated. Regardless of symptoms, begin first-line drug therapy with ACE inhibitors or ARBs (or, if these are not tolerated, hydralazine and nitrates) as well as β-blockers in patients who are not volume overloaded. Add loop diuretics and digoxin in patients with NYHA classes II, III, and IV heart failure and aldosterone antagonists in those with class III and IV heart failure. Monitor potassium and renal function. Consult a cardiologist in patients with severe heart failure who may require hospitalization for inotropic agents; placement of ICD devices, pacemakers, or left ventricular assist devices; or cardiac transplantation. Recognize that anticoagulation for patients with depressed ejection fractions remains controversial. Teach patients to participate in their own care by encouraging them to exercise and to monitor their diet, medical regimen, and weight.

CLINICAL BOTTOM LINE

68. American College of Cardiology/American Heart Association Task Force on Practice Guidelines (Committee to Revise the 1995 Guidelines for the Evaluation and Management of Heart Failure). ACC/AHA Guidelines for the Evaluation and Management of Chronic Heart Failure in the Adult: Executive Summary. Circulation. 2001;104:2996-3007. [PMID: 11739319]
69. American College of Cardiology. ACC/AHA 2005 Guideline Update for the Diagnosis and Management of Chronic Heart Failure in the Adult: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (Writing Committee to Update the 2001 Guidelines for the Evaluation and Management of Heart Failure): developed in collaboration with the American College of Chest Physicians and the International Society for Heart and Lung Transplantation: endorsed by the Heart Rhythm Society. Circulation. 2005;112:e154-235. [PMID: 16160202]
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What do professional organizations recommend with regard to the care of patients with heart failure?

In 2001, the ACC/AHA published guidelines for the Evaluation and Management of Chronic Heart Failure in the Adult (68), and these were updated in 2005 (69) and again in 2009 (1).

In addition to the ACC/AHA guidelines, other important guidelines include the Heart Failure Society of America 2006 Comprehensive Heart Failure Practice Guideline (70) and the Department of Veterans Affairs/Veterans Health Administration 2003 guidelines relating to the pharmacologic management of chronic heart failure (71).

What measures do stakeholders use to evaluate the quality of care for patients with heart failure?

The Centers for Medicare & Medicaid Services (CMS) have started a Physician Quality Reporting Initiative (PQRI) program, through which clinicians can report a designated set of quality measures on claims for services and earn bonus payments. Of the current measures in the PQRI program, 2 relate to heart failure. The first is similar to the Ambulatory Care Quality Alliance measure on the use of ACE inhibitors or ARBs, calling for use of these agents in patients older than 18 years with a diagnosis of heart failure and left ventricular dysfunction. The second measures use of β-blocker therapy in the same population.

In addition, the Agency for Healthcare Research and Quality is using quality indicators to measure the hospital admission rate for heart failure, and CMS has begun the public reporting of hospital-level 30-day mortality for patients with heart attack and heart failure.

Hospital readmission rates within 30 days of discharge as well as documentation of discharge teaching and instructions are also performance measures that are evaluated by several regulatory agencies.

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in the clinic

Tool Kit

Heart Failure

PIER Modules

www.pier.acponline.org

Access the PIER modules on heart failure and percutaneous coronary intervention from the American College of Physicians. PIER modules provide an evidence-based, electronic resource for clinical recommendations and links to patient information material at the point of care.

Patient Information

www.annals.org/intheclinic/toolkit-hf.html

Download copies of the Patient Information sheet that appears on the following page for duplication and distribution to your patients.

Quality Improvement Tools

www.ihi.org/ihi/search/searchresults.aspx?searchterm=heart+failure+tools&searchtype=basic

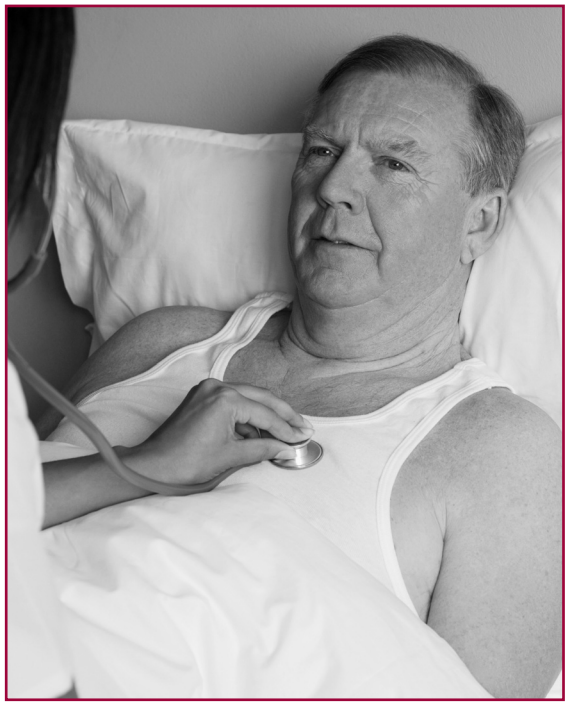
Links to a variety of helpful tools for managing various aspects of heart failure, compiled by the Institute for Healthcare Improvement.

www.cardiologyinoregon.org/information/information.html#toolkit

Resources from the Oregon Heart Failure GAP Toolkit, part of an American College of Cardiology project in 3 states to improve heart failure care.

THINGS YOU SHOULD KNOW ABOUT HEART FAILURE

- Heart failure, which is sometimes called congestive heart failure, is when the heart can't pump as well as it should. Because the heart has a hard time getting blood to the rest of the body, patients with heart failure can feel weak and tired.
- In some patients with heart failure, fluid (edema) builds up in the lungs and parts of the body, making it hard to breathe and causing swelling in the legs.
- Heart failure can be caused by many different conditions that directly or indirectly affect the heart. People with high blood pressure, diabetes, high cholesterol, and coronary artery disease can develop heart failure. Treating these conditions may prevent heart failure.
- Treating heart failure means working together with your doctor to control salt in your diet, watching your weight, and taking all your medications every day. It's important to keep your regular doctor appointments.
- Heart failure affects nearly 5 million adults, and 550 000 new cases are diagnosed each year. It is more common in older people but can occur at any age. Although there is no cure yet, heart failure is very treatable, and millions of Americans lead a full life by managing their condition through medications and by making healthy changes in their lifestyles.



Heart Failure Symptoms

- Breathlessness during activity, at rest, or while sleeping
- Wheezing or coughing that may be dry or may produce white or pink blood-tinged phlegm
- Swelling in the feet, ankles, legs, or abdomen or unexplained weight gain
- A constant lack of energy and difficulty performing everyday activities
- A sense of having a full or sick stomach
- A feeling like the heart is racing or pounding
- A feeling the heart is skipping beats or occasionally pounding very hard

For More Information

ACP®
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Internal Medicine | *Doctors for Adults*

Web Sites With Good Information on Heart Failure

www.doctorsforadults.com/images/healthpdfs/heartfail.pdf
American College of Physicians

www.americanheart.org/presenter.jhtml?identifier=1486
American Heart Association

www.nhlbi.nih.gov/health/dci/Diseases/Hf/HF_WhatIs.html
National Heart, Lung, and Blood Institute

Patient Information

CME Questions

MKSAP
MEDICAL KNOWLEDGE *Self-Assessment Program*

1. A 40-year-old woman is evaluated for 2 months of progressive dyspnea on exertion, orthopnea, and lower-extremity edema. She has no other medical problems and takes no medications, including over-the-counter drugs, and she does not use illicit drugs. She does not smoke cigarettes and rarely drinks alcohol. There is no family history of heart disease.

   On physical examination, she is afebrile. Blood pressure is 120/80 mm Hg, and pulse is 80/min. Estimated central venous pressure is 8 cm H_2O. Her lungs are clear. Cardiac examination reveals a regular rhythm, an S_3, and no murmurs. She has mild ankle edema. Chest radiograph shows mild vascular congestion. Electrocardiogram shows normal sinus rhythm. Initial laboratory evaluation reveals a normal hemoglobin level and metabolic profile, including thyroid studies.

   Which is the most appropriate initial diagnostic test?

   A. B-type natriuretic peptide level
   B. Echocardiography
   C. Radionuclide ventriculography
   D. Stress test

2. A 48-year-old man is evaluated in the emergency department for dyspnea on exertion and paroxysmal nocturnal dyspnea for 3 days. He has a history of type 2 diabetes mellitus and hypertension but no other medical problems. He does not smoke cigarettes. He currently takes metformin, lisinopril, and low-dose aspirin.

   On physical examination, he is afebrile. Blood pressure is 130/80 mm Hg, pulse is 100/min, and respiration rate is 20 breaths/min; BMI is 40 kg/m^2. Jugular veins are distended. Cardiac examination reveals a normal S_1 and S_2, the presence of an S_3, and a regular rate and rhythm with no murmurs. The point of maximum impulse is not displaced, and there are no heaves. Pulmonary auscultation discloses crackles at the bilateral lung bases. There is mild bilateral edema to the shins. Laboratory studies reveal a serum creatinine level of 76.3 µmol/L (1.0 mg/dL) and a B-type natriuretic peptide level of 100 ng/L. The electrocardiogram shows only sinus tachycardia, without pathologic Q waves or suspicious ST changes. Chest radiograph is pending.

   Which is the most likely diagnosis?

   A. Acute heart failure
   B. Acute pulmonary embolism
   C. Cor pulmonale
   D. Recent myocardial infarction

3. A 60-year-old woman is evaluated for follow-up after hospitalization 2 weeks ago for pulmonary edema and volume overload that readily resolved with intravenous diuretics. She is currently feeling well without edema or shortness of breath. Stress echocardiography done in the hospital had negative results for ischemia and showed an ejection fraction of 60% and no significant valvular abnormalities. She has a history of hypertension, hyperlipidemia, and chronic atrial fibrillation. She takes metoprolol (75 mg twice daily), hydrochlorothiazide, warfarin, aspirin, and pravastatin.

   On physical examination, she is afebrile. Blood pressure is 150/90 mm Hg and pulse is 50/min. Jugular veins are not distended, and her lungs are clear. Cardiac examination shows an irregularly irregular rhythm with variable intensity of the S_1 with no murmurs. There is no edema.

   Which is the most appropriate adjustment to her treatment?

   A. Add candesartan
   B. Add digoxin
   C. Change hydrochlorothiazide to furosemide
   D. Increase metoprolol dose

4. A 70-year-old woman is evaluated for a 1-month history of dyspnea on exertion and fatigue. She can still perform activities of daily living, including vacuuming, grocery shopping, and ascending 2 flights of stairs carrying laundry. She has a history of hypertension, mild chronic obstructive pulmonary disease, and smoking. Her medications are lisinopril, hydrochlorothiazide, and albuterol as needed.

   On physical examination, she is afebrile. Blood pressure is 110/80 mm Hg and pulse is 70/min. Jugular veins are not distended. There is a grade 2/6 holosystolic murmur at the left sternal border that radiates to the axilla, which was not noted during an examination 1 year ago. Rate and rhythm are regular, S_1 and S_2 are normal, and there is no S_3. The lung sounds are distant but clear without wheezing, and there is no edema. Laboratory studies show normal hemoglobin and thyroid-stimulating hormone levels. Electrocardiogram shows low voltage and left-axis deviation. Echocardiogram shows an ejection fraction of 35%, global hypokinesis, and mild mitral regurgitation. Chest radiograph shows flattening of the diaphragms but is otherwise normal.

   Which is the most appropriate treatment?

   A. Amlodipine
   B. Carvedilol
   C. Digoxin
   D. Losartan
   E. Spironolactone

Questions are largely from the ACP's Medical Knowledge Self-Assessment Program (MKSAP, accessed at http://www.acponline.org/products_services/mksap/15/?pr31). Go to www.annals.org/intheclinic/ to obtain up to 1.5 CME credits, to view explanations for correct answers, or to purchase the complete MKSAP program.