II HEART FAILURE

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Definition

Heart failure is a clinical syndrome resulting from a structural or functional cardiac disorder that impairs the ability of the ventricle to fill with or eject blood to meet the needs of the body. This syndrome, which is a constellation of signs and symptoms, is primarily manifested by dyspnea, fatigue, fluid retention, and decreased exercise tolerance. Heart failure may result from disorders of the pericardium, the myocardium, the endocardium, valvular structures, or the great vessels of the heart or from rhythm disturbances. It is important to emphasize that not all patients with heart failure symptoms have similar cardiac structural abnormalities. Indeed, the major thrust of an initial evaluation of a patient with heart failure is to define the cardiac abnormalities responsible for the symptoms.

Classification

Heart failure has been classified in many ways. One useful framework involves describing the underlying cardiomyopathy, which frequently will suggest the etiology [see Table 1 and Figure 1]. Some examples of the World Health Organization (WHO) classification include ischemic cardiomyopathy, hypertrophic or restrictive cardiomyopathy, and idiopathic dilated cardiomyopathy. In the United States, the most common cause of heart failure is ischemic cardiomyopathy from coronary artery disease (CAD).

Another practical approach for classification is to divide patients with heart failure into those with primarily systolic dysfunction and those with diastolic dysfunction. For the clinician, this usually means assessing the patient’s left ventricular ejection fraction (LVEF), most commonly with echocardiography. Patients with systolic heart failure typically have a low LVEF (usually less than 40% to 45%), a dilated left ventricular cavity, and a reduced cardiac output because of diminished contractility of the myocardium. In contrast, patients with diastolic heart failure have a normal LVEF and normal contractility, but there is impaired filling of the heart secondary to a variety of pathophysiologic abnormalities.

Despite an increased understanding of the etiologies and pathophysiology of heart failure and advancements in treatment, morbidity and mortality remain unacceptably high for the majority of patients stricken with this disorder. Most experts agree that earlier recognition of the syndrome or better identification of patients at risk for heart failure may be our best hope for the future reduction of heart failure’s death toll. This is analogous to the concerted efforts to screen for cancer at its earliest stages, before the disease can defy therapy. Consequently, the committee charged with revising the American College of Cardiology/American Heart Association (ACC/AHA) Guidelines for the Evaluation and Management of Heart Failure took the bold step of developing a new classification for patients with heart failure. These guidelines can be obtained from the ACC or AHA Web sites: http://www.acc.org/clinical/statements.htm and http://my.americanheart.org/portal/professional/guidelines.

The ACC/AHA classification emphasizes the evolution and progression of heart failure; it defines four stages of the disorder [see Table 2 and Figure 2]. Stage A identifies patients who are at high risk for developing heart failure but who have no apparent structural abnormality of the heart. This includes patients with hypertension, diabetes, or CAD; patients with a history of rheumatic fever, alcohol abuse, or exposure to cardiotoxic drugs; and patients with a family history of cardiomyopathy. Stage B denotes patients with a structural abnormality of the heart but in whom symptoms of heart failure have not yet developed. This includes patients found to have left ventricular hypertrophy or dilatation, a decreased LVEF, or valvular disease, as well as patients with prior myocardial infarction. Stage C refers to patients with a structural abnormality of the heart and symptoms of heart failure. This would include patients with dyspnea, fatigue, or fluid overload, as well as patients with a prior diagnosis of heart failure who are receiving treatment that has relieved their symptoms. Importantly, once patients have had symptoms of heart failure, they remain in stage C even if they subsequently experience clinical improvement. Stage D includes the patient with end-stage heart failure that is refractory to standard treatment. Typical patients include those who require frequent hospital admissions for heart failure, are awaiting a heart transplant, are being supported with intravenous agents or mechanical assist devices, or are receiving hospice care for end-stage heart failure.

The ACC/AHA classification is a departure from the traditional New York Heart Association (NYHA) classification, which characterizes patients by symptom severity. Patients with heart failure may progress from stage A to stage D, but never the reverse. In contrast, many patients with NYHA class IV symptoms can be restored to class II with appropriate therapy. The ACC/AHA classification highlights the importance of known risk factors and structural abnormalities in the development of heart failure. Additionally, it reinforces the concept that heart failure is a progressive disease whose onset can be prevented, or its progression halted, by early identification and intervention.

Epidemiology

Heart failure is one of the major public health problems in the United States today, both in terms of the number of patients affected and health care dollars spent. Nearly five million patients have heart failure, and almost 500,000 patients are diagnosed with the disease each year. Estimated direct and indirect costs for heart failure came to $21 billion in 2001, more than 5% of that year’s health care budget; annual spending on drugs for heart failure treatment is about $500 million. Hospitalizations for heart failure increased by 159% from 1979 to 1998, and this trend will likely continue as the United States population ages.

Heart failure is primarily a disease of the elderly. Approximately 6% to 10% of people older than 65 years have heart failure, and roughly 80% of patients hospitalized with heart failure are older than 65 years. More Medicare dollars are spent on heart failure than on any other disease, and heart failure is the most common Medicare diagnosis-related group.
Table 1  Examples of Descriptive and Etiologic Classifications of Heart Failure

<table>
<thead>
<tr>
<th>Classification Scheme</th>
<th>Disorder or Disease Process</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>By disorder</td>
<td>Dilated cardiomyopathy</td>
<td>Dilatation and impaired function of left ventricle or both ventricles; multiple etiologies: ischemia, valvular disease, infectious process, inflammatory process, toxins, familial/genetic cause, idiopathic</td>
</tr>
<tr>
<td></td>
<td>Hypertrophic cardiomyopathy</td>
<td>Hypertrophy of left ventricle or both ventricles, often asymmetrical and involving the interventricular septum; often associated with mutations in sarcoplasmic proteins; associated with arrhythmias and sudden death</td>
</tr>
<tr>
<td></td>
<td>Restrictive cardiomyopathy</td>
<td>Usually associated with normal systolic function and impaired diastolic function; can be idiopathic or associated with infiltrative diseases, such as amyloidosis, sarcoidosis, and endomyocardial fibrosis</td>
</tr>
<tr>
<td></td>
<td>Arrhythmogenic right ventricular cardiomyopathy</td>
<td>Replacement of myocardium with fatty tissue; can involve left ventricle as well; associated with ventricular arrhythmias; may have a genetic component</td>
</tr>
<tr>
<td>By underlying disease process</td>
<td>Ischemic heart disease</td>
<td>Secondary to coronary artery disease</td>
</tr>
<tr>
<td></td>
<td>Valvular disease</td>
<td>Caused by primary valvular disease</td>
</tr>
<tr>
<td></td>
<td>Hypertension</td>
<td>Usually associated with left ventricular hypertrophy; can involve systolic and/or diastolic dysfunction</td>
</tr>
<tr>
<td></td>
<td>Diabetes mellitus</td>
<td>Associated with systolic and/or diastolic dysfunction and left ventricular hypertrophy, even independent of coexisting hypertension or coronary artery disease</td>
</tr>
<tr>
<td></td>
<td>Inflammatory/infectious disease</td>
<td>Systolic dysfunction from myocarditis; multiple infectious etiologies, both viral (e.g., coxsackievirus, echovirus, HIV) and bacterial (rheumatic fever)</td>
</tr>
<tr>
<td></td>
<td>Metabolic disorders</td>
<td>Associated with endocrine abnormalities (e.g., hyperthyroidism, hypothyroidism), electrolyte deficiencies (potassium, magnesium), nutritional deficiencies (e.g., beriberi), and glycogen storage disease (e.g., Pompe disease, Gaucher disease)</td>
</tr>
<tr>
<td></td>
<td>General systemic disease</td>
<td>Associated with connective tissue diseases (e.g., systemic lupus erythematosus, rheumatoid arthritis) and infiltrative diseases (e.g., sarcoidosis, amyloidosis)</td>
</tr>
<tr>
<td></td>
<td>Muscular dystrophies</td>
<td>Includes Duchenne, Becker, and myotonic muscular dystrophies</td>
</tr>
<tr>
<td></td>
<td>Neuromuscular disease</td>
<td>Includes Friedreich ataxia and Noonan syndrome</td>
</tr>
<tr>
<td></td>
<td>Toxins</td>
<td>Associated with alcohol and cocaine abuse, treatment with cardiotoxic chemotherapeutic agents (e.g., anthracyclines), and radiation therapy</td>
</tr>
<tr>
<td></td>
<td>Tachycardia</td>
<td>Associated with uncontrolled tachycardias (e.g., atrial fibrillation and other supraventricular tachycardias)</td>
</tr>
<tr>
<td></td>
<td>Genetic/familial disorders</td>
<td>Associated with a family history of cardiomyopathy and/or sudden death; many cardiomyopathies previously designated as idiopathic may fall into this category</td>
</tr>
<tr>
<td></td>
<td>Pregnancy</td>
<td>Manifests in peripartum period</td>
</tr>
</tbody>
</table>

It is important to recognize that heart failure has diverse causes and affects diverse populations. Until recently, this diversity was not reflected in the composition of heart failure trials in the United States, which typically enrolled middle-aged white men with ischemic cardiomyopathy. In fact, the heart failure population in the United States includes significant numbers of women, elderly persons, and members of racial minorities—and these patients tend to have different forms of heart failure. For example, in an estimated 20% to 50% of patients with heart failure, ventricular systolic function is preserved (i.e., the patients have diastolic heart failure), and these patients are more likely to be elderly women.20–23

Etiology

CAD is responsible for roughly two thirds of cases of heart failure in the United States.24 Coronary ischemia or infarction can lead to heart failure through a variety of mechanisms: acute coronary syndromes or infarction can cause acute heart failure in an otherwise normal heart; likewise, repeated insults of ischemia or infarction can cause a chronic cardiomyopathy. Moreover, many patients with diastolic heart failure have underlying CAD.

Ventricular dysfunction can result from a multitude of non-ischemic causes [see Table 1]. These include hypertension; diabetes; valvular disease; arrhythmias; myocardial toxins; myocarditis from a variety of infectious etiologies (including HIV); and hypothyroidism. Infiltrative causes of ventricular dysfunction, which are usually associated with restrictive cardiomyopathy, include amyloidosis, hemochromatosis, and sarcoidosis. Myocardial systolic dysfunction for which there is no apparent cause is labeled idiopathic cardiomyopathy. Over the past several years, there has been increased recognition that many of these so-called idiopathic dilated cardiomyopathies are familial; a number of centers are actively focusing on the identification of the genetic irregularities responsible for the abnormal phenotypes.25

Pathophysiology

There is no single, simple model that effectively explains the syndrome of heart failure; currently, the consensus view integrates multiple pathophysiologic models to explain the complex cascade of events leading to this clinical syndrome.26 The different structural, functional, and biologic changes that culminate in heart failure have led to a variety of treatment...
modalities to target this array of causative factors. For example, for many years, beta blockers were contraindicated in patients with heart failure because the disorder was thought to be primarily a result of decreased myocardial contractility that would worsen with negative inotropic therapy. However, we have come to realize the central role of pathologic sympathetic activation in heart failure—the maladaptive mechanisms that lead to vasoconstriction, arrhythmias, and ventricular remodeling (see below). This model explains the therapeutic benefits of beta blockade.

The hemodynamic model of heart failure concentrated on the role of increased load on a failing ventricle; this conceptual approach led to the successful use of vasodilators and inotropes. Later, the neurohumoral model of heart failure identified the critical importance of the renin-angiotensin-aldosterone axis and the sympathetic nervous system in the progression of car-

Figure 1  The different cardiac morphologies in heart failure. (a) Normal; (b) dilated cardiomyopathy; (c) hypertrophic cardiomyopathy; (d) diastolic dysfunction.
with a dilated, poorly contracting heart. CAD or ischemia may also result in dyspnea, and peripheral edema identical to that seen in patients with congestive heart failure especially during exercise. Ventricular pressures are elevated for some time after systolic failure despite normal systolic function, cardiac output is limited and the left ventricle dilates and becomes more globular, increasing diastolic filling pressures. Functional mitral regurgitation often occurs as the left ventricle dilates and becomes more globular, increasing diastolic filling pressures. Remodeling seems to beget more remodeling. Functional mitral regurgitation often occurs as the left ventricle dilates and becomes more globular, increasing diastolic filling pressures. Remodeling seems to beget more remodeling.

Arrhythmias often contribute to myocardial dysfunction and are an unwelcome side effect of heart failure. Supraventricular arrhythmias, particularly atrial fibrillation, often mask systolic or diastolic dysfunction in a previously asymptomatic patient. In addition, intraventricular conduction delays and bundle branch block are often present in patients with heart failure. Abnormal ventricular conduction, particularly left bundle branch block, has significant detrimental hemodynamic effects. In addition to contributing to worsening heart failure, ventricular arrhythmias are likely a direct cause of death in many of these patients; the rate of sudden cardiac death in persons with heart failure is six to nine times that seen in the general population.

These pathophysiologic models do not easily explain diastolic heart failure. In the 20% to 50% of patients who have heart failure despite normal systolic function, cardiac output is limited by abnormal filling and disordered relaxation of the ventricles, especially during exercise. Ventricular pressures are elevated for a given ventricular volume, leading to pulmonary congestion, dyspnea, and peripheral edema identical to that seen in patients with a dilated, poorly contracting heart. CAD or ischemia frequently compounds the impairment of ventricular performance in patients with diastolic heart failure, who typically are elderly women with hypertension, diabetes, and obesity.

Diagnosis

Stage A

The first step in the diagnosis of heart failure is to identify patients who are at risk for developing the syndrome; this concept was part of the reasoning behind the new ACC/AHA staging system. Patients in stage A are those with CAD, hypertension, diabetes, a history of alcohol abuse or exposure to cardiotoxic drugs (e.g., certain chemotherapeutic agents, cocaine), a history of rheumatic fever, or a family history of cardiomyopathy or sudden death. In these high-risk patients, reversible risk factors should be aggressively treated to prevent heart failure from developing.

![Figure 2](https://example.com/figure2.png)
Stage B patients have asymptomatic, structural heart disease. Echocardiography is easily the best diagnostic tool to uncover left ventricular hypertrophy or dilatation, valvular disease, or wall motion abnormalities indicative of previous myocardial infarction. Patients in stage B represent a significant portion of the heart failure population and constitute a key opportunity for intervention. In a community-based survey, less than half of patients with moderate or severe systolic or diastolic dysfunction, as defined by echocardiographic parameters, had recognized heart failure. At this time, the ACC/AHA guidelines do not recommend routine screening echocardiography for the large number of patients at risk for the development of heart failure. Nonetheless, a class IIA indication is given for noninvasive evaluation of left ventricular function in patients with a strong family history of cardiomyopathy or in those exposed to cardiotoxic therapies.

**Stages C and D**

Stages C and D fit the traditional definition of heart failure. Patients in stage C or D usually present with decreased exercise tolerance, fluid retention, or both. Initial assessment of these patients should focus on the structural abnormality leading to heart failure, as well as evaluation of its etiology. Initial testing should include a 2-D echocardiogram with Doppler flow studies, a chest x-ray, electrocardiography, and laboratory studies, including urinalysis, complete blood count, serum chemistries, liver function studies, and thyroid-stimulating hormone measurement. These tests serve primarily to exclude other potential causes of dyspnea or fatigue. In patients with dyspnea, measurement of serum brain natriuretic peptide (BNP) may aid in the diagnosis; marked elevation of BNP levels suggests that the dyspnea is cardiac rather than pulmonary in origin. Strong consideration should be given to excluding significant CAD, because CAD is the leading cause of left ventricular dysfunction. The ACC/AHA guidelines strongly encourage that patients with heart failure be evaluated with coronary angiography rather than noninvasive testing, even if they do not have a known history of CAD; the guidelines cite the fact that noninvasive testing can often lead to inaccurate results in patients with cardiomyopathies (e.g., perfusion defects or wall motion abnormalities in patients with a nonischemic cardiomyopathy). Nonetheless, some argue that there is little evidence that revascularization changes outcome or prognosis in patients with left ventricular dysfunction and that it should therefore be used only to relieve angina.

Several clinical parameters are useful for the subsequent evaluation and management of heart failure. Patients’ weights should be measured in the office, and patients should be taught to follow their weights at home to assess for fluid retention. Office evaluation of jugular venous pressure, hepatomegaly, reflex, the presence of a gallop rhythm, and peripheral edema can aid in initial diagnosis and can guide the need for diuresis. In addition, these signs of heart failure may be prognostically important.

**Diastolic Heart Failure**

There is no precise definition of diastolic heart failure; the diagnosis is usually made by a clinician who recognizes the typical signs and symptoms of heart failure despite the finding of normal systolic function (i.e., a normal LVEF) on an echocardiogram. Doppler echocardiographic techniques can also aid in establishing the diagnosis of diastolic dysfunction.

**Treatment**

Treatment for heart failure is keyed to the stage of the syndrome as defined by the recent ACC/AHA guidelines [see Table 3]. Treatment in all stages is aimed at preventing or palliating the remodeling process [see Pathophysiology, above]. In addition, therapy in stages C and D is intended to relieve the disabling symptoms of heart failure.

**Stage A**

The goal of treatment in stage A is to prevent structural heart disease. This is achieved by controlling risk factors (e.g., hypertension, CAD, diabetes mellitus, hyperlipidemia, smoking, alcohol ingestion, and use of cardiotoxic drugs), which lowers the incidence of later cardiovascular events. For example, effective treatment of hypertension decreases left ventricular hypertrophy and cardiovascular mortality; it can also reduce the incidence of heart failure by 30% to 50%. Diabetes deserves particular attention because diabetes patients have a high incidence both of CAD and of heart failure in the absence of CAD; diabetes causes many detrimental biochemical and functional cardiac changes independent of ischemia. ACE inhibitors and angiotensin receptor blockers (ARBs) have assumed a major role in risk reduction for diabetic patients (see below). Studies have shown that in asymptomatic high-risk patients with diabetes or vascular disease who have no history of heart failure or left ventricular dysfunction, treatment with these agents yields significant reductions in death, myocardial infarction, and stroke or delays the first hospitalization for heart failure.

**Stages B, C, and D**

The goals of therapy for patients with heart failure and a low LVEF are to decrease the progression of disease and the number of hospitalizations, improve symptoms and survival, and

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**Table 3** Treatment of Heart Failure

| Stage | Treat hypertension | Encourage smoking cessation | Treat lipid disorders | Encourage regular exercise | Discourage alcohol intake, illicit drug use | Prescribe ACE inhibitors if appropriate | All measures used for stage A | ACE inhibitors if appropriate (see text) | Beta blockers if appropriate | All measures used for stage A | Drugs for routine use: | ACE inhibitors | Beta blockers | Digitalis | Dietary salt restriction | All measures used for stages A, B, and C | Mechanical assist devices | Heart transplantation | Continuous (not intermittent) I.V. inotropic infusions for palliation | Hospice care |
|-------|-------------------|-----------------------------|----------------------|--------------------------|-------------------------------------|-----------------------------------------|-------------------------------|--------------------------------------|---------------------------------|--------------------------|-------------------|----------------|-----------|-----------------|------------------------|-----------------|-----------------|-------------------------------------------------|------------|

ACE—angiotensin-converting enzyme

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November 2003 Update
minimize risk factors. Simple interventions can help patients control their disease. For example, basic habits of moderate sodium restriction, weight monitoring, and adherence to medication schedules serve to prevent hospitalizations for rapid fluid overload. Other frequent causes of decompensation in heart failure include anemia, arrhythmias (especially atrial fibrillation), noncompliance with medications and diet, or the use of nonsteroidal anti-inflammatory drugs (NSAIDs).52-55

ACE inhibitors are recommended for all patients in stages B, C, and D. By decreasing the conversion of angiotensin I to angiotensin II, ACE inhibitors minimize the multiple pathophysiologic effects of angiotensin II, such as vasoconstriction and fibrosis. ACE inhibitors (but not ARBs) also decrease the degradation of bradykinin, a substance that causes vasodilation and natriuresis. In patients with heart failure, ACE inhibitors have been shown to improve survival and cardiac performance, to decrease symptoms and hospitalizations, and to decrease or slow the remodeling process.58-60

Currently, it is not clear whether all ACE inhibitors are equally effective in all forms of heart failure. There are few data from controlled trials, for example, about the efficacy of ACE inhibitors in diastolic heart failure. Moreover, although several guidelines have emphasized the need to maximize the dose of ACE inhibitor to target levels (rather than using blood pressure alone to guide dose titration), current recommendations underscore the need to add beta blockers to the regimen of patients in stage C early in the course of treatment, even if target ACE inhibitor doses have not been achieved.

Angiotensin receptor blockers What is the role of ARBs in heart failure? These agents block the effects of angiotensin II at the angiotensin II type 1 receptor site. ACC/AHA guidelines recommend the use of ARBs only in patients who cannot tolerate ACE inhibitors because of cough or angioedema14; the guidelines stress that ARBs are comparable to ACE inhibitors but are not superior.61-63 Since publication of the guidelines,

### Table 4 Pharmacotherapy of Heart Failure

<table>
<thead>
<tr>
<th>Category</th>
<th>Drug (Trade Name)</th>
<th>Dosage</th>
<th>Comment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Loop diuretics</td>
<td>Bumetamide (Bumex)</td>
<td>0.5–1 mg q.d. or b.i.d.</td>
<td>Titrated to achieve dry weight; carefully monitor serum potassium and creatinine levels</td>
</tr>
<tr>
<td></td>
<td>Furosemide (Lasix)</td>
<td>20–40 mg q.d. or b.i.d.</td>
<td>Titrated to achieve dry weight; carefully monitor serum potassium and creatinine levels</td>
</tr>
<tr>
<td></td>
<td>Torsemide (Demadex)</td>
<td>10–20 mg q.d. or b.i.d.</td>
<td>Titrated to achieve dry weight; carefully monitor serum potassium and creatinine levels</td>
</tr>
<tr>
<td>ACE inhibitors</td>
<td>Captopril (Capoten)</td>
<td>6.25 mg t.i.d.</td>
<td>Carefully monitor serum potassium and creatinine levels</td>
</tr>
<tr>
<td></td>
<td>Enalapril (Vasotec)</td>
<td>2.5 mg b.i.d.</td>
<td>Carefully monitor serum potassium and creatinine levels</td>
</tr>
<tr>
<td></td>
<td>fosinopril (Monopril)</td>
<td>5–10 mg</td>
<td>Carefully monitor serum potassium and creatinine levels</td>
</tr>
<tr>
<td></td>
<td>Lisinopril (Prinivil, Zestril)</td>
<td>2.5–5 mg</td>
<td>Carefully monitor serum potassium and creatinine levels</td>
</tr>
<tr>
<td></td>
<td>Quinapril (Accupril)</td>
<td>10 mg b.i.d.</td>
<td>Carefully monitor serum potassium and creatinine levels</td>
</tr>
<tr>
<td></td>
<td>Ramipril (Altace)</td>
<td>1.25–2.5 mg</td>
<td>Carefully monitor serum potassium and creatinine levels</td>
</tr>
<tr>
<td>Beta blockers</td>
<td>Bisoprolol (Zebeta)</td>
<td>1.25 mg</td>
<td>Titrate dosage up over 2- to 4-week intervals, carefully monitoring for signs and symptoms of fluid overload</td>
</tr>
<tr>
<td></td>
<td>carvedilol (Coreg)</td>
<td>3.125 mg b.i.d.</td>
<td>Titrate dosage up over 2- to 4-week intervals, carefully monitoring for signs and symptoms of fluid overload</td>
</tr>
<tr>
<td></td>
<td>Metoprolol tartrate (Lopressor)</td>
<td>6.25 mg b.i.d.</td>
<td>Titrate dosage up over 2- to 4-week intervals, carefully monitoring for signs and symptoms of fluid overload</td>
</tr>
<tr>
<td></td>
<td>Metoprolol succinate extended release (Toprol-XL)</td>
<td>12.5–25 mg</td>
<td>Titrate dosage up over 2- to 4-week intervals, carefully monitoring for signs and symptoms of fluid overload</td>
</tr>
<tr>
<td>Digitalis glycosides</td>
<td>Digoxin (Lanoxin)</td>
<td>0.125–0.25 mg</td>
<td>Narrow therapeutic window; monitor levels carefully in older patients and those with renal insufficiency</td>
</tr>
<tr>
<td>Aldosterone inhibitors</td>
<td>Spironolactone (Aldactone)</td>
<td>25 mg</td>
<td>50 mg q.d. was maximum dosage used in RALES trial79; use carefully with concurrent ACE inhibitor or ARB; carefully monitor serum potassium and creatinine levels; use if potassium &lt; 5.0 mmol/L, creatinine &lt; 2.5 mg/dl</td>
</tr>
<tr>
<td>Angiotensin receptor blockers</td>
<td>Candesartan (Atacand)</td>
<td>8 mg</td>
<td>Use if patients have cough or angioedema on ACE inhibitor</td>
</tr>
<tr>
<td></td>
<td>Irbesartan (Avapro)</td>
<td>75 mg</td>
<td>Use if patients have cough or angioedema on ACE inhibitor</td>
</tr>
<tr>
<td></td>
<td>Losartan (Cozaar)</td>
<td>25 mg</td>
<td>Use if patients have cough or angioedema on ACE inhibitor</td>
</tr>
<tr>
<td></td>
<td>valsartan (Diovan)</td>
<td>80 mg</td>
<td>Use if patients have cough or angioedema on ACE inhibitor</td>
</tr>
</tbody>
</table>

ACE—angiotensin-converting enzyme ARB—angiotensin receptor blocker RALES—Randomized Aldosterone Evaluation Study

Medical Therapy
Pharmacologic treatment of heart failure routinely includes diuretics, angiotensin antagonists, beta blockers, and digoxin; spironolactone or inotropes may be beneficial in some cases [see Table 4].

**Diuretics** In symptomatic patients in stage C and stage D, diuretics are often the first drugs prescribed to decrease fluid overload and congestive symptoms. Loop diuretics are most often given to these patients, either as maintenance therapy or on an as-needed basis. Loop diuretics can be combined with thiazides to optimize diuresis.30-57

**ACE inhibitors** ACE inhibitors are recommended for all patients in stages B, C, and D. By decreasing the conversion of angiotensin I to angiotensin II, ACE inhibitors minimize the
however, several key trials have reported successful intervention with ARBs in stage B and C patients.\textsuperscript{64,66} The role of ARBs in patients already on beta blockers, with or without an ACE inhibitor, remains to be elucidated. Symptomatic patients who cannot tolerate ACE inhibitors or ARBs, usually because of renal insufficiency, may benefit from a combination of hydralazine and isosorbide dinitrate for afterload reduction.\textsuperscript{66}

**Beta blockers** Although it was once taught that beta blockers were contraindicated in heart failure secondary to systolic dysfunction, multiple studies have now shown an impressive effect of these drugs on many aspects of heart failure and at all stages of the syndrome. The primary action of these agents is to counteract the harmful effects of the increased sympathetic nervous system activity in heart failure. Beta blockers improve survival, ejection fraction, and quality of life; they also decrease morbidity, hospitalizations, sudden death, and the maladaptive effects of remodeling.\textsuperscript{67,68} Long-term placebo-controlled trials have shown improvement in systolic function and reversal of remodeling after 3 to 4 months of treatment with beta blockers.\textsuperscript{69-71} A recent analysis showed that even in the sickest of heart failure patients, beta-blocker therapy was well tolerated and led to a decrease in mortality and hospitalizations as early as 14 to 21 days after initiation of therapy.\textsuperscript{72} However, clinicians should be extremely cautious about starting beta blockers in patients with significant reactive airway disease, in diabetic patients with frequent episodes of hypoglycemia, or in patients with bradycardias or heart block who do not have a pacemaker implanted.

In the United States, two beta blockers are specifically approved for treatment of heart failure: carvedilol and long-acting metoprolol. Beta blockers should be started at the lowest possible dose and titrated up slowly at 2- to 4-week intervals. Patients should be closely monitored for worsening of symptoms or fluid retention, which can sometimes occur early in therapy with these agents. If patients do have exacerbations during initiation of beta blockade, diuretic therapy can be increased, and titration of the beta blocker can proceed more slowly.

**Digoxin** Digoxin has long been a mainstay in the treatment of symptomatic patients with left ventricular dysfunction, despite a lack of data from clinical trials showing benefit. A large randomized study demonstrated that digoxin was successful in decreasing hospitalization for heart failure—an important clinical end point—but did not decrease mortality.\textsuperscript{73} Recent post hoc analysis of data from this trial showed that in the patients randomized to receive digoxin therapy, mortality may have been higher in women than in men.\textsuperscript{74} It is hypothesized that the therapeutic window for digoxin may be different in men and women, with women perhaps needing a lower dose of the drug.\textsuperscript{75} Indeed, data suggest that digoxin improves morbidity as effectively at low serum concentrations (< 0.09 ng/ml) as at higher levels, and with less toxicity.\textsuperscript{76} Clinicians should carefully monitor all patients for signs and symptoms of digoxin toxicity, especially those patients who are elderly or have renal dysfunction. Physicians and patients should also keep in mind that digoxin interacts with numerous other drugs.

**Spironolactone** Another relatively old drug with new data to support its use in heart failure is the aldosterone antagonist spironolactone. Because of the activation of the renin-angiotensin-aldosterone axis, which is incompletely suppressed by ACE inhibitors, patients with heart failure have increased circulating levels of aldosterone. This leads to sodium retention and potassium loss. Aldosterone also works locally within the myocardium, contributing to hypertrophy and fibrosis in the failing heart.\textsuperscript{77} A large randomized trial has shown that the addition of low-dose spironolactone (25 mg daily) to standard treatment reduces morbidity and mortality in patients with NYHA class III and IV heart failure (stage C and D patients).\textsuperscript{78}

**Intravenous inotropes** Patients with refractory heart failure (stage D patients) often require intermittent intravenous inotropic therapy to aid in diuresis and to improve symptoms. No survival benefit has been demonstrated with inotropic treatment. These agents have received a class IIb indication in the ACC/AHA guidelines\textsuperscript{79}—that is, they are regarded as palliative.

**Diastolic heart failure** Despite the large number of patients with primarily diastolic heart failure, few clinical trials have addressed the management of these cases. Physiologic principles used to guide treatment in these patients include control of blood pressure, heart rate, myocardial ischemia, and blood volume.\textsuperscript{80}

**Revascularization and surgical therapy** Patients in all stages of heart failure must be evaluated for CAD. Angioplasty and surgical revascularization improve ischemic symptoms and can lead to improved ejection fraction and decreased incidence of sudden death.\textsuperscript{81}

Clinical trials to investigate the role of surgical interventions in halting or reversing the remodeling process are now underway. Such interventions include mitral valve repair or replacement, mechanical devices to reduce wall stress, and surgical excision of infarcted tissue.\textsuperscript{82}

Cardiac transplantation remains the only definitive treatment for stage D patients, but it is available only to roughly 2,500 patients a year in the United States.\textsuperscript{83} Left ventricular assist devices are available to support patients waiting for heart transplant. There is growing evidence supporting the use of these devices as destination therapy for stage D patients, many of whom are not eligible for cardiac transplantation.\textsuperscript{84}

**Implanted devices**

**Biventricular Pacing Systems**

Many heart failure patients have intraventricular conduction delays that may contribute to altered myocardial contractility or dyssynchrony. Biventricular pacing is a novel therapy for patients with left ventricular systolic dysfunction, particularly those with a left bundle branch block. The goal of this therapy is to restore the usual pattern of electrical activation of the left ventricle and thereby restore ventricular synchrony. Pacing leads are placed in the right atrium and the right ventricle and into a cardiac vein in the lateral wall of the left ventricle via the coronary sinus. There is evidence that with restored ventricular synchrony from a biventricular pacing system, the remodeling process is halted and reversed. Trials have shown that implantation of a biventricular pacemaker results in decreased ventricular size and volumes, improved ventricular function, and less mitral regurgitation. This has led to improved exercise tolerance, decreased hospitalizations, and improved quality of life.\textsuperscript{85-88} Although individual randomized trials have not shown a mortality benefit for biventricular pacing, a recent meta-analysis of four of the largest trials to date showed a 51% decrease in death
from progressive heart failure. In addition, a large clinical trial of biventricular pacing in patients with heart failure was stopped early because resynchronization therapy was found to confer a statistically significant benefit regarding the combined end point of mortality and hospitalization.

Cardioverter-Defibrillators

The use of implantable cardioverter-defibrillators (ICDs) for the primary prevention of sudden death in patients with left ventricular dysfunction has grown enormously in recent years. There is increasing evidence that ICD placement reduces mortality in patients with ischemic cardiomyopathy, regardless of whether they have nonsustained ventricular arrhythmias. The role of these devices in patients with heart failure of a nonischemic cause has yet to be elucidated and is the subject of several ongoing trials.

Prognosis

Despite many advances in the management of heart failure, this disorder remains life-threatening. Symptomatic heart failure continues to confer a worse prognosis than the majority of cancers in the United States, with 1-year mortality averaging 45%. Nonetheless, it is difficult to discuss the prognosis of heart failure as a whole, because an individual patient’s likelihood of survival is related to the cause of the heart failure, as well as multiple other clinical factors. For example, given the same severity of heart failure symptoms, an 85-year-old woman with ischemic cardiomyopathy would have a lower likelihood of survival than a 45-year-old man with idiopathic cardiomyopathy. One study of 1,230 patients with cardiomyopathy found that survival was significantly worse in patients with cardiomyopathy from ischemia, infiltrative disease, cardiotoxic chemotherapy, HIV infection, or connective tissue disease than in patients with idiopathic cardiomyopathy.

There are conflicting data about the prognosis of diastolic heart failure. However, recent studies have shown that mortality in these cases may be as high as in systolic heart failure, and hospitalization rates are equal.

It is also important for clinicians to remember that a low LVEF is not universally predictive of poor outcome. In patients referred for transplantation, survival has correlated more closely with other variables—notably, peak exercise oxygen consumption. One prospectively validated model for predicting survival in patients with severe heart failure incorporates LVEF with six other clinical factors: presence of coronary disease, resting heart rate, mean arterial blood pressure, presence of intraventricular conduction delays, serum sodium concentration, and peak exercise oxygen consumption. These tools can be used to stratify patients according to risk and to make the most appropriate use of modern therapies and treatment modalities.

How can we improve the prognosis of patients with heart failure? A recent report from the Framingham Heart Study has shown promising evidence of increasing survival after the diagnosis of heart failure [see Figure 3]. To further this trend, we must work toward widespread implementation of the therapies known to decrease morbidity and mortality in heart failure. We must also investigate more completely the impact of medical therapy on the survival of patients with diastolic heart failure. There should be continued efforts to increase the number of traditionally underrepresented patients (e.g., women and minorities) enrolled in heart failure trials. Finally, in keeping with the emphasis of the ACC/AHA guidelines, we must concentrate on identifying and treating those patients at greatest risk for heart failure to prevent it from occurring.

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Acknowledgment

Figure 1  Alice Y. Chen.