Medical Management of Advanced Heart Failure

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Heart failure has emerged as a major health challenge, increasing in prevalence as age-adjusted rates of myocardial infarction and stroke decline. Affecting 4 to 5 million people in the United States with more than 2 million hospitalizations each year, heart failure alone accounts for 2% to 3% of the national health care budget. Developments heralded in the news media increase public expectations but focus on decreasing disease progression in mild to moderate stages or supporting the circulation mechanically for limited periods in end-stage disease. Most of the burden of this disease is borne between these 2 boundaries by patients with advanced heart failure, a quarter of the diagnosed heart failure population.

Advanced heart failure is defined as symptoms limiting daily life (New York Heart Association class III or IV) despite previous therapy with angiotensin-converting enzyme (ACE) inhibitors, diuretics, digoxin, and more recently β-adrenergic blocking agents when tolerated. As the syndrome of heart failure with preserved left ventricular ejection fraction (LVEF) is still undergoing definition, advanced heart failure with LVEF of 25% or less is the focus of this review (Table 1).

Data Sources
We searched MEDLINE for all articles containing the term advanced heart failure that were published between 1980 and 2001; EMBASE was searched from 1987-1999; Best Evidence from 1991-1998, and Evidence-Based Medicine from 1995-1999. The Cochrane Library also was searched for critical reviews and meta-analyses of congestive heart failure.

Data Extraction Data quality was determined by publication in peer-reviewed literature or inclusion in professional society guidelines.

Data Synthesis A primary focus for care of advanced heart failure is ongoing identification and treatment of the elevated filling pressures that cause disabling symptoms. While angiotensin-converting enzyme inhibitors and β-adrenergic agents can slow disease progression and prolong survival, titration and tolerability often present challenges. Most patients are not eligible for surgical intervention but do benefit from a medical regimen tailored to individual clinical and hemodynamic profiles and from heart failure management programs that reduce rehospitalization. Survival ranges from 80% at 2 years for patients rendered free of congestion to less than 50% at 6 months for patients with refractory symptoms, in whom end-of-life options may include hospice care and inactivation of implantable defibrillators.

Conclusions Current management of advanced heart failure is based more on consensus than on randomized trials. Systematic investigation should address not only new therapies but also strategies for selecting and optimizing therapies already available.

Context Advanced heart failure, defined as persistence of limiting symptoms despite therapy with agents of proven efficacy, accounts for the majority of morbidity and mortality in heart failure.

Objective To review current medical therapy for advanced heart failure.

See also Patient Page.
smaller trials, trials of milder heart failure, consensus guidelines, and clinical experience both published and personal. Data quality for extraction was determined by publication in peer-reviewed literature or inclusion in professional society guidelines.

Evaluation of Advanced Heart Failure

Search for Potentially Reversible Factors. Evaluation of primary cause has been detailed elsewhere. Potentially reversible factors should be sought repeatedly. Atrial fibrillation is present in 25% to 50% of patients with advanced heart failure. Left ventricular ejection fraction and clinical status frequently improve after therapy, with continuing controversy regarding the benefits of restoring sinus rhythm vs diligent rate control. Although digoxin may control resting rate, control of ambulatory rate generally requires ß-adrenergic blocking agents or amiodarone.

Heavy alcohol consumption can cause and aggravate heart failure although modest use has been associated epidemiologically with a lower incidence. Obesity not only exacerbates but also can cause cardiomyopathy that may reverse dramatically after major weight loss although weight loss is rarely achieved. Anemia and pulmonary emboli exacerbate heart failure. Thyroid abnormalities should be sought, particularly in patients receiving amiodarone. Common viral infections often aggravate heart failure for several weeks even after resolution of viral symptoms.

Coronary artery disease is present in 50% to 70% of patients with advanced heart failure. In such patients, the quest for reversible ischemia creates many questions. Revascularization is supported by controlled data for LVEF ranging from 35% to 50% and by registry data for LVEF that is less than 35% with dominant ischemic symptoms. Although noninvasive testing is frequently performed to demonstrate ischemic regions for revascularization, there is no controlled evidence for screening or intervention without angiography.

Left ventriculectomy for nonischemic cardiomyopathy (popularized by Batista) is no longer actively performed because poor outcomes were found. For large dyskinetic regions after infarction, aneurysmectomy may be undertaken. A proposed modification with endocardial patch placement, described by Beyersdorf et al., is under clinical investigation. Mitral valve repair or replacement is sometimes considered for severe valvular regurgitation secondary to dilated heart failure. Surgical morbidity can be high for patients debilitated from advanced heart failure, for which patient indications for valvular surgery have not been established.

Elucidation of Symptoms. Effective therapy requires that clinicians thoroughly understand what patients perceive to be the most limiting aspects of their lives. Regular review of specific activities including dressing, climbing stairs, getting the mail, and pushing a grocery cart provide better information than the New York Heart Association class definitions. Symptoms of advanced heart failure are dominated by those related to congestion, a reflection of elevated filling pressures. High left-sided filling pressures cause shortness of breath or coughing when lying down (orthopnea) or immediate dyspnea on light exertion, such as dressing or walking across a room. Dyspnea occurring after sustained exercise reflects multiple hemodynamic, pulmonary, and skeletal muscle abnormalities. Elevated right-sided filling pressures can cause uncomfortable edema or ascites, anorexia, early satiety, abdominal fullness, and discomfort when bending. Symptoms attributable to low resting cardiac output are less specific and usually include lack of energy and fatigue. Daytime sleepiness or difficulty concentrating may reflect disturbed nocturnal sleep, severely reduced cerebral perfusion, depression, or boredom due to withdrawal from usual activities.

Definition of Hemodynamic Profile. The approach to advanced heart failure has been simplified by the consider-
Identification of elevated filling pressures in chronic heart failure relies heavily on the symptom of orthopnea and the finding of elevated jugular venous pressure. Rales are absent in more than 80% of patients with chronically elevated filling pressures due to compensation of the pulmonary lymphatics. Residual interstitial fluid rarely compromises oxygenation but often causes marked distress from the sensation of restricted inspiration. Edema is relatively insensitive to elevated filling pressures in populations younger than 70 years, occurring in only about 25% of patients, while in older patients, edema is often caused by local factors unrelated to central venous volume. A third heart sound is present all the time in some patients with heart failure and is never detected in others, but changing intensity in an individual suggests changing filling pressures.

Skill in assessing jugular venous pressures requires regular practice and is the most important aspect of the physical assessment of volume status both in hospital and in clinic. Jugular venous pressure in centimeters is conveniently measured as vertical distance from the top of the pulsations down to the sternal angle. Estimated right atrial pressure of less than 5 cm from the sternal angle. Estimated right atrial pressure of less than 5 cm from the sternal angle. The height of the jugular venous pressure above the sternal angle in centimeters + 5 cm between the sternal angle and right atrium. When using right-sided filling pressures to estimate the left atrial pressure,26 the Valsalva maneuver,27 and intensity of the pulmonic component of the second sound provide additional information to practiced examiners.

The most accessible evidence of perfusion is blood pressure. Too often recorded casually, the blood pressure requires careful auscultation to determine the width of the pulse pressure. In patients with age and disease severity typical of transplantation candidates, proportional pulse pressure of less than 25% [(systolic – diastolic blood pressure)/systolic blood pressure] suggests a cardiac index, which is calculated as cardiac output in liters per minute divided by body surface area in square meters (L·min⁻¹·m⁻²), below 2.2 L·min⁻¹·m⁻².21 This estimate requires further validation, particularly in elderly patients with less compliant vessels. Patients who fall asleep during questions or have pulsus alternations may have severely reduced perfusion. Cool temperature of the forearms and legs may be more specific for low cardiac output than cold hands and feet. Low perfusion is suspected when patients with volume overload develop symptomatic hypotension even with low-dose ACE inhibitors.

In a series of 486 patients admitted to a heart failure service with low LVEF, 67% of those with clinical evidence of decompensation appeared on initial evaluation as profile B (wet and warm), while 28% appeared as profile C (cold and dry), and only 5% appeared to be cold and dry.28 The rates of death and of cardiac transplantation at 1 year were twice as high in patients presenting as profile C compared with those with presenting as profile B. Although the simplification into these profiles has helped guide therapy and prognosis, many patients admitted with congestion may actually have borderline perfusion, a wet and lukewarm profile.

**Design of Therapy**

The first priority of treatment for advanced heart failure is relief of symp-
toms, without which enthusiasm is limited for decreasing disease progression and prolonging survival, the fundamental goals for therapy of heart failure with few or no symptoms. It will be assumed that patients presenting with advanced heart failure have already undergone attempted therapy with diuretics, ACE inhibitors, in most cases digoxin, and may have previous or current therapy with β-adrenergic blocking agents (FIGURE 2).

Focus on Filling Pressures. In the past, heart failure was often viewed as a disorder of low cardiac output. Focus on acute maximization of cardiac output led to therapies that increased mortality. Increasingly, however, therapy for heart failure has focused on reducing the elevated filling pressures that can occur with or without resting hypoperfusion. Because the dominant symptoms are those of congestion, relief of resting symptoms requires reduction of elevated filling pressures.

Benefits of reducing filling pressures extend, however, beyond initial symptomatic improvement. Mitral regurgitation usually takes more than 50% of total left ventricular stroke volume in patients asymptomatic at rest and is most effectively reduced and redistributed forward by therapies that reduce left ventricular filling pressures and the effective regurgitant orifice. Elevated filling pressures not only carry a high cost for myocardial oxygen consumption but compromise the gradient for myocardial perfusion, often increasing angina in heart failure due to coronary artery disease. Neurohormonal activation and its decrease are strongly related to levels of left ventricular filling pressures. Exercise capacity is improved with reduction of filling pressures below the levels usually achieved for relief of resting symptoms. Left ventricular filling pressures are the major factor leading to elevated pulmonary pressures and right ventricular dysfunction. Malnutrition in heart failure and circulating cytokine levels relate closely to elevated right-sided filling pressures and hepatosplanchnic congestion. Reductions of elevated filling pressures and associated natriuretic peptide levels are associated with improved outcome.

Therapy for Hemodynamic Profiles

Profile B: Wet and Warm. The estimated hemodynamic profile guides initial therapy. For patients without evidence of elevated filling pressures or hypoperfusion (profile A), further therapy is adjusted for the longer-term goals of maintaining stable volume status and preventing disease progression. For patients who are profile B (wet and warm), therapy needs to dry them out.

Assuming that they are already receiving ACE inhibitors, the major change is enhancement of the diuretic regimen. Patients with profile B can often be treated as outpatients when fluid overload is recent, diuretic responses have been well-characterized, and good follow-up is available. During hospitalization for more complex cases, symptom relief can often be achieved by intravenous loop diuretics in boluses or infusions, sometimes supplemented with other diuretics such as metolazone. Initial improvement in congestive symptoms can be ac-

### Figure 2. Stepped Therapy for Heart Failure

<table>
<thead>
<tr>
<th>Disease Severity</th>
<th>Medications</th>
<th>Activity</th>
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<tbody>
<tr>
<td>Asymptomatic</td>
<td>Diuretics to Treat Fluid Retention</td>
<td>As Tolerated Exercise Training</td>
</tr>
<tr>
<td>Symptomatic</td>
<td>ACE Inhibitor or Angiotensin II Receptor Blocker if Severe Cough or Angioedema With ACE Inhibitor</td>
<td></td>
</tr>
<tr>
<td>Advanced</td>
<td>If Needed, Use Torsemide, Intermittent Metolazone Add Spironolactone if Normal Potassium-Handling</td>
<td></td>
</tr>
<tr>
<td>Refractory</td>
<td>Consider 2000 mL Fluid Restriction</td>
<td></td>
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</tbody>
</table>

The step diagram demonstrates addition of therapies in relation to the clinical severity of heart failure with reduced left ventricular ejection fraction. Angiotensin-converting enzyme (ACE) inhibitors are prescribed at every level of disease severity, but they may have to be withdrawn for symptomatic hypotension or progressive renal dysfunction in 10% to 30% of patients approaching end-stage disease, as indicated by the asterisk. Angiotensin receptor–blocking agents (ARBs) are a reasonable alternative for patients who cannot tolerate ACE inhibitors due to angioedema or severe cough but they are not appropriate for patients intolerant to ACE inhibitors due to symptomatic hypotension, renal failure, or hyperkalemia. β-Adrenergic blocking agents are prescribed for patients with mild to moderate symptoms of heart failure, but they are not initiated in patients with severe symptoms of heart failure unresponsive to stabilization with other therapies. Diuretics are prescribed to maintain fluid balance, with spironolactone added in patients with severely symptomatic disease when renal function and potassium handling are preserved. Fluid retention persisting despite high-dose loop diuretic therapy may be better managed with torsemide, a loop diuretic with better absorption. Metolazone effectively potentiates loop diuretic effects, but regular use should be avoided due to severe electrolyte depletion.

When severe symptoms persist, patients should be reevaluated to diagnose and treat persistent congestion. Some patients may benefit from addition of nitrates with or without hydralazine. Transplantation and mechanical assist devices are relevant to only a very small population with advanced heart failure. Restriction of sodium and fluid intake is increasingly required as heart failure becomes more severe. Exercise is recommended for all patients except those with severe resting dyspnea. Heart failure management programs are most cost-effective in patients at high risk for repeated heart failure hospitalizations, but they may be useful at every stage of disease.
celerated by intravenous vasodilators such as nitroglycerin. Nesiritide, a human recombinant form of the endogenous brain natriuretic peptide, has been shown to relieve symptoms rapidly. This newly released drug is used with a bolus and fixed dose infusion, with or without invasive hemodynamic monitoring. It acts primarily as a vasodilator although it may also potentiate the effect of diuretics in some patients. As with other vasodilators, the major risk is hypotension, which persists slightly longer than with nitroglycerin, due to the longer half-life of 18 minutes. It is not known whether vasodilator infusions have benefits beyond early symptom relief.

For patients with profile B, inotropic therapy is not often necessary and in fact may be detrimental. In fact, in a recent study that demonstrated no benefit from milrinone infusion, the baseline blood pressure was 120 mm Hg, so many patients would likely have been profile B. Patients whose outpatient clinical status had been stable while receiving a β-blocker or ACE inhibitors may need to continue it if perfusion is adequate and volume balance can be easily restored, but those whose doses had recently been increased should resume the dose that was previously tolerated.

Profile C: Wet and Cold. For patients with clinical hypoperfusion, it is usually necessary to “warm up in order to dry out.” For these patients in whom reflex responses support the failing circulation, β-blockers and ACE inhibitors may need to be withdrawn until stabilization is achieved, particularly for patients with symptomatic hypotension. Although improvement of systemic perfusion may often require intravenous therapy, for most patients low cardiac output is associated with high systemic vascular resistance with predictable improvement with vasodilator therapy alone (Table 1). There is considerable controversy about the relative roles of vasodilators and inotropic vasodilator agents such as dobutamine, low-dose dopamine, and milrinone.

The intravenous vasodilator best studied in advanced heart failure is nitroprusside, a direct nitrovasodilator. Filling pressures are lowered rapidly through venous and arterial vasodilation, with increases in cardiac output, which in turn improve response to intravenous diuretics. Titration is usually monitored invasively using a pulmonary artery catheter. The optimal hemodynamic profile achieved is then maintained by adjusting oral vasodilator agents, usually combinations of ACE inhibitors, nitrates, and sometimes hydralazine, as nitroprusside is weaned. Monitored nitroprusside infusion rarely causes symptomatic hypotension but is occasionally complicated by suspected cyanide toxicity, which increases with dose, duration, and hepatic dysfunction. Intravenous nitroprusside causes both arterial and venodilation in this population, usually at higher doses than nitroprusside. Successful transition to an effective oral vasodilator regimen is straightforward. Intravenous nesiritide may also be effective for vasodilation, but experience with this new agent is limited.

Intravenous inotropic infusions are associated with increased risk for ischemic events and tachyarrhythmias. In a controlled trial of hospitalized patients without hypotension, milrinone caused more tachyarrhythmias and symptomatic hypotension than placebo, so it should not be used for the indication of hypotension. Dobutamine is less likely to cause hypotension and is much less expensive than milrinone but also increases heart rate risk and of arrhythmias. Another major limitation of inotropic therapy is the complexity of adjusting oral regimens as infusions are weaned. Prolonged physiologic effects of these infusions prior to discharge may mask inadequacy of the diuretic regimen and intolerance to vasodilator doses, setting the stage for readmission. This may be more likely with milrinone due to its long half-life, further prolonged in the presence of renal dysfunction. For this reason, it is recommended that patients receiving inotropic infusions remain hospitalized for at least 48 hours after inotropic discontinuation. There is also concern that admission for inotropic infusions as “tune-ups” may create inotropic dependence.

Patients who appear dependent on inotropic infusions should undergo careful re-evaluation to make sure that filling pressures are optimally reduced. When hypotension prevents weaning of inotropic agents, ACE inhibitors may need to be stopped. In some patients, hydralazine, particularly in combination with nitrates, may facilitate inotropic weaning.

Inotropic infusions are frequently used during hospitalization, in part because of initial convenience. Although the benefits of routine inotropic infusions often may not justify the risks, they can be life-saving while definitive procedures are being arranged for patients with rapidly progressive hemodynamic collapse. When hemodynamic status is initially unclear in patients with severe symptoms, intravenous inotropic infusion may provide temporary stability until a more definitive profile can be defined. For chronic decompensation, brief inotropic therapy may be appropriate in those patients with high baseline blood urea nitrogen levels who have not demonstrated effective diuresis in response to repeated high dose intravenous loop diuretics with combined thiazides. In general, use of current inotropic agents in heart failure may be considered as “until” therapy: until diuresis, until resolution of transient conditions such as pneumonia, until transplantation, or until death, as discussed below.

Profile L: Cold and Dry. Patients with profile L, those with low cardiac output without clinical evidence of elevated filling pressure, may be surprisingly stable clinically and often do not present with urgent symptoms. Those admitted as cold and dry often have unappreciated congestion. Unless they have subnormal filling pressures or excessive vasodilation, they often do not improve acutely with adjustments of oral therapy. Inotropic infusions may lead to inotropic dependence and tachyphylaxis. Gradual introduction of β-adrenergic blocking agents, if tolerated, may be associated with later clinical improvement, which has also been observed with amiodarone. Benefits may be greater when initial heart rates are
high.\textsuperscript{57} No trials have targeted this small subgroup.

**Clinical Assessment vs Hemodynamic Monitoring to Guide Therapy**

The clinical assessment used to define profiles (Figure 1) is frequently a sufficient guide for initial therapy although bedside skill in estimating hemodynamics has been challenged.\textsuperscript{40} The usual goals of clinically guided therapy are normal jugular venous pressure, resolution of orthopnea and edema, systolic blood pressure of at least 80 mm Hg and proportional pulse pressure of at least 25\%, stable renal function, and the ability to walk the ward without dizziness or dyspnea. Invasive hemodynamic monitoring is often used when more precise measures of filling pressures, perfusion, and systemic vascular resistance are desired. Urgent hemodynamic monitoring guides initial intervention in critical situations during which therapies must be provided rapidly to avoid circulatory collapse. Hemodynamic monitoring may be particularly helpful when another condition complicates management (such as pulmonary disease), the initial profile is not clear from clinical assessment and response, multiple therapies need to be adjusted simultaneously, therapy guided by empiric assessment is ineffective to maintain symptom relief, or intravenous inotropic agents cannot be weaned.

Pulmonary artery catheterization is routinely performed to evaluate pulmonary vascular resistance in potential transplantation candidates. Leaving the catheter in while redesigning therapy over a 24- to 72-hour period has often been followed by prolonged stabilization without transplantation.\textsuperscript{36,43} This experience has been generalized in some centers to other patients with severe symptoms. When therapy is tailored using a strategy of hemodynamic monitoring with clinical assessments, the goals are to approach pulmonary wedge pressure of 16 mm Hg or less and right atrial pressure of 8 mm Hg or less, first with intravenous vasodilators, then with oral therapies. Although not a primary target of therapy, systemic vascular resistance measurement may guide titration of vasodilators vs diuretics to reduce filling pressures. Invasive hemodynamic measurement may allow rapid achievement of lower filling pressures, but it is not known whether this leads to better long-term outcomes.

The availability of newer techniques to estimate hemodynamics may enhance individualization of therapy. The noninvasive bioimpedance device to assess filling pressures and cardiac output and the implanted hemodynamic monitor for home transmission of filling pressures are undergoing evaluation. Brain natriuretic peptide (BNP) levels, which are increased by left-ventricular distention, provide an index of volume status\textsuperscript{38} somewhat as hemoglobin A\textsubscript{1C} provides an index of blood glucose control. Titration of therapy to BNP levels has been proposed\textsuperscript{49} but not tested in a large advanced heart failure population. It remains to be determined as to what extent these monitoring technologies will influence interventions and alter outcomes.

**Cardiorenal Syndrome in Heart Failure**

Among patients experiencing the late stages of advanced heart failure, the most common reason that symptoms cannot be relieved, despite aggressive management, is the recently recognized cardiorenal syndrome. Some patients, often those with baseline renal impairment, demonstrate progressive decrements in renal function even as diuresis relieves symptoms. This may be most common with long-standing volume overload, right ventricular dysfunction, and high baseline diuretic requirements. Aggravated renal dysfunction occurs in approximately 25\% of patients hospitalized with heart failure, at times forcing choices between treating renal function and providing symptom relief.\textsuperscript{50,51}

The term *prerenal* does not clarify either the mechanism or the solution of the cardiorenal syndrome. It was at one time assumed to reflect low cardiac output put from excessively reduced filling pressures during diuresis. When measured, filling pressures usually still exceed the optimal levels needed to maintain cardiac output.\textsuperscript{50} Cardiorenal interactions may involve altered balance of vasodilating and vasoconstricting hormones triggered by changes in cardiopulmonary pressures. Higher creatinine and blood urea nitrogen levels are associated with a lower likelihood of maintaining freedom from congestion\textsuperscript{52} and a greater likelihood of rehospitalization and death.\textsuperscript{50}

Optimal clinical status may be maintained for many patients at a creatinine and blood urea nitrogen level higher than levels during volume overload. In some patients, renal function slowly improves during chronic maintenance of a lower volume state. The cardiorenal syndrome is 1 of the major factors leading to frequent inotropic infusions, which can relieve congestion temporarily, but the impasse usually reappears once inotropic therapy is weaned. Chronic discontinuation of ACE inhibitors with transition to hydralazine-nitrate combinations may become necessary when serum creatinine levels continue to rise higher than 3 mg/dL (265.2 µmol/L) and/or blood urea nitrogen levels rise higher than 80 to 100 mg/dL (28.6-35.7 mmol/L). Under these conditions, angiotensin receptor antagonists cannot substitute for ACE inhibitors due to similar renal effects. In rare cases with otherwise good hemodynamic stability, chronic peritoneal or hemodialysis may be considered. The solution to the cardiorenal syndrome awaits better understanding of the mechanisms.

**Discharge Medical Regimen Diuretics.** Identification and aggressive treatment of elevated filling pressures in advanced heart failure is the major difference between heart failure regimens before and after referral to tertiary care centers. The average patient referred with severe congestive symptoms undergoes approximately 4 L of net diuresis.\textsuperscript{52} The diuretic regimen to maintain optimal volume status is lower than that required to initiate net
diuresis. When weight gain suggests volume retention, the usual dose is supplemented with transient dose doubling or intermittent addition of a thiazide, in a flexible patient-guided program. Patients with recurrent volume retention despite high maintenance doses of furosemide may benefit from more reliable absorption of the more costly loop diuretic torsemide (TABLE 2). Spironolactone, the aldosterone inhibitor, was associated with a 33% decrease in rehospitalization in the Randomized Aldactone Evaluation Study trial of advanced heart failure. Potential mechanisms include inhibition of aldosterone-related fibrosis and cardiac and vascular remodeling, and preservation of electrolyte balance, with a modest diuretic effect apparent in some patients. After the 25-mg dose was associated with a 13% severe hyperkalemia in the pilot trial, the larger trial excluded patients with creatinine levels of more than 2.0 mg/dL (176.8 µmol/L), stopped routine potassium supplementation, and monitored electrolyte levels with a vigilance hard to maintain in general practice. The usual patient with advanced heart failure has labile renal function predisposing to hyperkalemia and the risk of hyperkalemia is further increased by diabetes, high ACE inhibitor doses, or combination therapy with angiotensin receptor–blocking agents. General use should be limited to patients requiring loop diuretics who have serum creatinine levels that are stable and lower than 2.0 mg/dL (176.8 µmol/L).

ACE Inhibitors and Other Oral Vasodilators. The vasodilator regimen merits reevaluation after the establishment of optimal volume status, when patients often become more sensitive to the hypotensive effects of vasodilators. For ACE inhibitors, the complex actions include both vasodilation, which can be acutely beneficial, and neurohormonal antagonism, which improves long-term prognosis but may decrease cardiac output and blood pressure when circulatory compensation stimulates the renin-angiotensin system. Captopril, a shorter-acting ACE inhibitor given 3 to 4 times daily, may be easier to initiate when difficulty is anticipated due to hypotension. ACE inhibitor doses may occasionally need to be decreased or stopped to allow weaning of intravenous inotropic agents. Between 10% and 30% of patients with advanced heart failure are unable to tolerate ACE inhibitors due to hypotension or renal function by the cardiorenal syndrome (see “Cardiorenal Syndrome in Heart Failure” section).

### Table 2. Common Medications for Advanced Heart Failure

<table>
<thead>
<tr>
<th>Medication</th>
<th>Initial Dose</th>
<th>Maximum Dose</th>
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<tbody>
<tr>
<td><strong>Loop diuretics</strong></td>
<td></td>
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</tr>
<tr>
<td>Furosemide</td>
<td>20-40 mg 1-2 times daily</td>
<td>Titrate up to 400 mg/d†</td>
</tr>
<tr>
<td>Bumetanide</td>
<td>0.5-1.0 mg 1-2 times daily</td>
<td>Titrate up to 10 mg/d</td>
</tr>
<tr>
<td>Torsemide</td>
<td>50 mg 1-2 times daily‡</td>
<td>Titrate up to 200 mg/d</td>
</tr>
<tr>
<td><strong>Supplemental thiazides</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Metolazone</td>
<td>1.25 mg/d ½ hour before loop diuretic dose</td>
<td>Intermittent use to restore stable weight, up to 5 mg twice daily</td>
</tr>
<tr>
<td>Hydrochlorothiazide</td>
<td>25-100 mg/d before loop diuretic dose</td>
<td>To use instead of metolazone if weaker effect is desired</td>
</tr>
<tr>
<td>Spironolactone (only with loop diuretics)</td>
<td>25 mg/d or every other day</td>
<td>25 mg twice daily, occasionally higher for refractory hypokalemia</td>
</tr>
<tr>
<td><strong>Angiotensin-converting enzyme inhibitors</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Captopril</td>
<td>6.25 mg twice daily</td>
<td>50-100 mg 4 times daily</td>
</tr>
<tr>
<td>Enalapril maleate</td>
<td>2.5 mg twice daily</td>
<td>10-20 mg twice daily</td>
</tr>
<tr>
<td>Fosinopril sodium</td>
<td>5-10 mg/d</td>
<td>40 mg/d</td>
</tr>
<tr>
<td>Lisinopril</td>
<td>2.5-5.0 mg/d</td>
<td>20-40 mg/d</td>
</tr>
<tr>
<td>Quinapril hydrochloride</td>
<td>10 mg twice daily</td>
<td>40 mg twice daily</td>
</tr>
<tr>
<td>Ramipril</td>
<td>1.25-2.5 mg/d</td>
<td>10 mg/d</td>
</tr>
<tr>
<td><strong>β-Blockers</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bisoprolol</td>
<td>1.25 mg/d</td>
<td>10 mg/d</td>
</tr>
<tr>
<td>Carvedilol</td>
<td>3.125 mg twice daily</td>
<td>25-50 mg twice daily</td>
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<tr>
<td>Metoprolol tartrate</td>
<td>6.25 mg twice daily</td>
<td>75 mg twice daily</td>
</tr>
<tr>
<td>Metoprolol CR/XL§</td>
<td>12.5-25 mg/d</td>
<td>200 mg/d</td>
</tr>
<tr>
<td><strong>Diabetes</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>0.125 mg every other day to 0.25 mg/d</td>
<td>No titration except to avoid toxic effects</td>
</tr>
<tr>
<td><strong>Other vasodilators</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Isosorbide dinitrate</td>
<td>10 mg 3 times daily</td>
<td>80 mg 3 times daily</td>
</tr>
<tr>
<td>Sublingual isosorbide</td>
<td>2.5 mg as occasion requires or prior to exercise to decrease dyspnea</td>
<td></td>
</tr>
<tr>
<td>Hydralazine</td>
<td>25 mg 3 times daily</td>
<td>150 mg 4 times daily</td>
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</table>

*Data are adapted from Hunt et al.†Titrate to achieve patient dry weight. Optional volume status may occasionally be higher than dry weight in the setting of disproportionate right ventricular failure or limitation of renal function by the cardiorenal syndrome (see “Cardiorenal Syndrome in Heart Failure” section).‡Usually substituted for furosemide after persistent or recurring fluid retention, so initial doses may be higher.§CR/XL indicates controlled-release/extended-release metoprolol succinate.©2002 American Medical Association. All rights reserved.
dysfunction.455 In such patients, angiotensin-receptor blockers are also contra-indicated, and a combination of hydralazine and nitrates is often recommended. For class III to IV heart failure, hydralazine-nitrate therapy has shown the same effect on heart failure end points as ACE inhibitors although ACE inhibitors reduced deaths occurring unexpectedly.55,56

Once a patient is stabilized and has been released from the hospital, ACE inhibitor doses can be increased as tolerated. Titration to the target doses used in clinical trials (150 mg captopril, 20 mg enalapril maleate, and 20-40 mg lisinopril)3,5,37,38 is recommended when tolerated. After the original ACE inhibitor trials, however, the overall regimen has expanded to include β-adrenergic blocking agents. Although every attempt should be made to advance beyond the starting doses, there is decreasing emphasis on arbitrary target doses.6,10 Maintenance of lower ACE inhibitor doses is often reasonable, particularly for elderly patients with borderline hypotension. Compared with lower doses, high doses of ACE inhibitors led to only a 1% reduction in the absolute number of annual events in the Assessment of Treatment with Lisinopril And Survival trial, a difference that was not reproduced in another trial.29

Hydralazine has been used effectively to wean some patients apparently dependent on intravenous inotropic infusions.44 Hydralazine may also be added to ACE inhibitors to increase vasodilation for hypertension or severely elevated systemic vascular resistance. Although hydralazine and nitrates are commonly combined, either can be used alone or in combination with ACE inhibitors.

Nitrates were the first vasodilators shown to improve outcome in chronic heart failure.60 For patients with advanced heart failure, nitrates are often added to ACE inhibitors for further reduction of measured filling pressures or to decrease dyspnea that occurs early with exertion despite good volume status. Although unsupported by commercial interest, the generic nitrate compounds are prescribed by many heart failure consultants to improve symptoms, with minimal adverse effects except headaches. A small controlled trial confirmed improved exercise capacity when nitrates are added to ACE inhibitors in advanced heart failure and suggested decrease in left ventricular dimensions.61

Digitalis Glycosides. Digitalis is recommended for heart failure that remains symptomatic despite ACE inhibitors, β-blockers, and diuretics. In the Digitalis Investigation Group trial, heart failure hospitalizations were decreased, most notably in patients at highest risk.62 Most patients with advanced heart failure receive digitalis unless contraindicated due to conduction system disease or renal failure. Although inotropic state can be increased acutely with high doses, the major benefit of digoxin is now attributed to autonomic effects seen at low doses.53

Neurohormonal Antagonism With β-Blockers. For patients who can be stabilized without evidence of congestion, the focus of further therapy is improvement of long-term outcome by decreasing disease progression and death. The 2 neurohormonal antagonist classes that slow disease progression are ACE inhibitors and β-blockers. ACE inhibitors are recommended for all stages of heart failure.6 Recent trials have expanded the more limited candidate population for β-blocking agents, demonstrating that even patients with LVEF of lower than 25% and severe symptoms frequently tolerate and benefit from cautious initiation of these agents.55,60 These patients were carefully selected, however, excluding those with obvious volume overload or recent intravenous infusions. When started, β-blockers often increase filling pressures and decrease cardiac output, so initiation is not recommended for those who are hemodynamically compromised. Either in or out of the hospital, patients on the edge of decompensation may be pushed into pulmonary edema or cardiogenic shock by any dose of β-blockers.

In patients who tolerate β-blockers, improvement in LVEF and hemodynamics often occurs after several months. Improvement correlates in part with reductions in elevated baseline heart rates.58 A strategy of short-term inotropic therapy to facilitate initiation of β-blocker therapy is under investigation in patients otherwise too unstable. It is not known whether the benefits of β-blocker therapy would be realized in this population and whether their magnitude would outweigh the known risks of inotropic therapy.

Target daily doses of 50 to 100 mg carvedilol or 200 mg controlled-release/extended-release metoprolol succinate (metoprolol CR/XL) achieved in selected trial populations are less often achieved in general use.63 Gradual up-titration is indicated when tolerated, but even low doses can improve LVEF and reduce the rate of rehospitalization.66 Clinical experience suggests increasing doses over longer intervals such as monthly when tolerability is a concern. Patients must receive detailed instructions regarding early signs of volume retention and the distinction between mild lassitude and circulatory collapse. Occasionally, severe depression can develop. Adjustment of other medications is frequently necessary during initiation of β-blocking agents. When blood pressure limits the recommended doses of ACE inhibitors and β-blocking agents, it is not known how they should be balanced although the general consensus is that the use of both agents at moderate doses is preferable to the use of either alone.6,10 The critical role of heart failure management programs is highlighted by the need for meticulous patient follow-up to achieve safe and effective titration of β-blocking agents.

Maintaining Stability

Hospital Discharge. Rehospitalization occurs in 30% to 50% of patients within 3 to 6 months after heart failure hospitalization.67 Failure to meet criteria for discharge may increase the rate of rehospitalization. Although there is strong pressure to discharge patients quickly, the last hospital day consumes fewer resources than the first day of rehospitalization. Criteria for dis-
charge include at least 24 hours of stable fluid status, blood pressure, and renal function on the oral regimen planned for home (Box). Patients should be free of dyspnea or symptomatic hypotension while at rest, washing, and walking on the ward. Patients who have received intravenous inotropic agents should be observed for at least 48 hours after weaning to avoid masking inadequacy or intolerability of the discharge regimen. Education should proceed throughout hospitalization.

Heart Failure Disease Management

Although most therapy for advanced heart failure reflects expert consensus, heart failure management has shown consistent benefits in historically controlled and prospective randomized studies, with a 25% to 75% decrease in hospitalizations. The magnitude of impact exceeds that demonstrated for any single drug, emphasizing the importance of individualized care. First appreciated in transplantation programs and clinical trials, multiple variations exist on the theme of intensive follow-up by specialized heart failure nurses who provide education and preemptive telephone contact to identify problems and allow patients the opportunity to ask questions. Benefit was not shown for regular follow-up care with a primary physician and nurse team, in which patient satisfaction improved but hospitalization rate increased. A recent meta-analysis indicates that hospitalization rates are reliably decreased by experienced heart failure physician-nurse teams making decisions but not by centralized nursing services providing patient contact but no intervention except through multiple primary providers. Meticulous monitoring and response to changing volume status is the most important aspect of ongoing care for advanced heart failure.

Patient education includes frequent review of a flexible diuretic plan adjusted according to daily weights and specific information on sodium restriction. Fluid restriction to 2 L daily may improve stability for patients with repeated fluid retention despite high-dose diuretics, particularly those with unappreciated high fluid intake previously. Although low serum sodium does not necessarily indicate excess water intake or respond to free water restriction in this population, it reflects intense neurohormonal activation such that patients may need to restrict fluid intake to maintain fluid balance as diuretics become less effective.

Vaccination for influenza and pneumonia are recommended. For patients without resting symptoms, regular exercise is strongly advised, such as a walking program outside or in enclosed shopping areas or stationary bicycle and treadmill exercise. The randomized controlled trials of exercise training in patients with heart failure have demonstrated remarkable improvements in function and reduced hospitalization rates, with indication that autonomic balance is improved. Formal exercise training is not currently reimbursed for patients with heart failure.

Adjunctive Therapies for Advanced Heart Failure

The scope of this review does not include detailed discussion of therapies not yet incorporated into guidelines. There is some consensus that evaluation and therapy for nocturnal respiratory disturbances should be pursued. Biventricular pacing to synchronize left and right ventricular contraction has improved functional capacity and quality of life in patients with QRS duration over 150 milliseconds, present in 20% to 30% of patients with advanced heart failure. Ongoing trials will help determine the role that this therapy will ultimately play in advanced heart failure. Insertion of implantable cardioverter defibrillators is recommended for patients who have had sustained ventricular arrhythmias or cardiac arrest, or inducible ventricular tachycardia if the prognosis for extended good quality of life remains otherwise good. Risk stratification remains difficult in other patients. Application of this technology to a broader heart failure population is being tested in ongoing trials.

Compromised nutrition represents complex interplays between gastrointestinal tract symptoms that decrease food intake and absorption, transition to a protein-wasting state associated with chronic inflammatory activation similar to many chronic diseases, and, less commonly, increased metabolic rate. Caloric supplements can be helpful when intake is low but rarely reverse malnutrition unless underlying factors also improve. Supplementation with micronutrients is under investigation. Erythropoietin with iron has been described to improve clinical status in patients with heart failure and moderate anemia.

Stress reduction techniques should be considered for patients with intrinsic and situational anxiety. Depression is increasingly recognized to decrease quality of life, functional capacity, and perhaps survival with
heart failure, but pharmacotherapy has not been studied in the population carrying both diagnoses.

**Prognosis of Advanced Heart Failure**

Survival ranges from 80% at 2 years for patients rendered free of congestion to less than 50% at 6 months for patients with refractory symptoms at rest. Clinical class, although imprecise, consistently provides a general estimate of prognosis. For patients with low LVEF, reported yearly mortality has been from 10% to 15% with stable class II symptoms, 15% to 25% for class III, and 30% to 50% or higher for class IV. Prognosis is usually described as worse with coronary artery disease, but the risk added by coronary artery disease may come from patients who also have diabetes. Once class III through IV symptoms have developed and LVEF is lower than 25%, its exact value is less important than ventricular dilation, which predicts higher mortality at every stage of disease. In a study of patients referred with class IV symptoms and LVEF lower than 25%, 2-year survival was 60% with left ventricular diastolic dimension less than 70 mm, but only 20% with dimension greater than 85 mm. The degree of preservation of right ventricular function also predicts outcome in advanced disease.

Prognosis at every stage is worsened by even modest degrees of renal insufficiency. Serum sodium concentration is a robust predictor of survival. Low serum–sodium levels indicate intense activation of reflex systems to preserve perfusion, although they can also be caused by chronic thiazide diuretic use. Multiple parameters of neurohormonal and cytokine activation predict outcome, including serum norepinephrine, endothelin, and tumor necrosis factor α, but these are not routinely measured. The bedside assay for brain natriuretic peptide correlates with clinical severity of heart failure and with prognosis. Broader use of BNP levels as a screening test is likely to increase identification of asymptomatic left ventricular dysfunction and of heart failure as the cause of unexplained dyspnea. For patients with known heart failure, it is not known how much prognostic information will be provided beyond that from routine clinical assessment.

Although often considered as one of the neurohormonal markers, BNP is released predominantly from the left ventricle under stress and closely reflects left ventricular filling pressures. Filling pressures have been shown to predict outcome, particularly when measured after adjustment of therapy. The elevation of filling pressure is also a major determinant of many other prognostic factors, including echocardiographic mitral inflow patterns, severity of mitral and tricuspid regurgitation, pulmonary artery systolic pressure, and right ventricular ejection fraction.

Measurements of functional capacity such as peak oxygen consumption from formal exercise testing are useful when following up with individual patients for more aggressive intervention such as cardiac transplantation, for adjusting exercise prescriptions, and for gauging ability to perform physical work. The 6-minute walk distance correlates generally with outcome and is easier to perform, but it is not precise enough for the preceding indications. Most of the predictive power of exercise tests comes from the highest and lowest ranges, which are frequently evident from a careful history and observation of the patient.

All parameters may be more predictive when reassessed after rigorous optimization of therapies within a disease management program. Clinical status remains a useful, perhaps sufficient, predictor for most advanced heart failure. Patients presenting with class IV symptoms who can be stabilized without evidence of congestion can be upgraded to a prognosis similar to that of class III patients. Using a simple congestion score of 0 through 5 at 1 month after hospitalization, with 1 point each for orthopnea, jugular venous distention, ankle edema, recent weight gain, or need for diuretic increase, showed patients with a score of 0 to have a 2-year survival of 87%, twice that of those with a score of 3 through 5.

Accurate prediction of survival is meaningful only for large populations. Even then, most estimates are based on populations with lower prevalence of implantable cardioverter defibrillators than the current 12% to 25% in advanced heart failure. Numerical estimates of survival on medical therapy are most relevant to those few eligible for high-risk intervention such as cardiac transplantation or trials of new assist devices. Most patients and families facing advanced heart failure need to understand that this disease is likely to be fatal and that the end may come unexpectedly. Once that is understood, those individuals who still demand specific numbers for life expectancy should receive generous estimates and encouragement to plan ahead for activities and events that provide meaning to their lives.

**Quality of Life With Advanced Heart Failure**

For many patients with advanced heart failure, quality of life is as important as anticipated survival. Some of the frustration with multiple assessment tools results from the limited impact of our current drug therapies on quality of life. Diuretic therapy, for which there is little trial data but universal acceptance of efficacy, may yield the most immediate and dramatic symptomatic improvement. Although ACE inhibitors have not consistently improved quality of life, they allow better maintenance of current quality of life, seldom perceived by patients as improvement. β-Adrenergic blocking agents have been associated with better quality of life than has placebo in some studies, but they often appear neutral despite marked improvements in LVEF. From anecdotal experiences, it seems likely that symptomatic improvement for some patients receiving long-term β-blocker therapy may be partly counterbalanced by severe fatigue or depression developing in a small proportion of patients.

Patients with heart failure can express preferences for perceived health vs length of survival. Patients with
New York Heart Association class I or II symptoms rarely wished to trade time or take significant risks for better health although most patients with class IV symptoms expressed willingness to trade more than half their remaining time or risk death by more than 50% so they could feel better. Preferences for quality over length of life correlated with jugular venous pressure elevation, dyspnea, and peak oxygen consumption.34 Some patients wanted survival at all costs despite poor quality of life. The responses suggest that an understanding of patient preferences should help guide selection of therapy for an individual and set parameters by which new therapies for advanced heart failure are evaluated.

Functional capacity, quality of life, or both improved early during therapy with some agents subsequently found to increase mortality, such as flosequinan, a vasodilator with some inotropic action, and the inotropic agents pimobendan and lasix.26 These medications were not developed further due to serious adverse events. Although there are currently no known agents for heart failure that produce sustained improvement in quality of life with a small increased risk of death, such an agent, if developed, might be a valuable option for the small population of patients with otherwise refractory heart failure symptoms.

End-Stage Heart Failure

Despite the multiple interventions shown to improve survival, heart failure remains a progressive disease. Fewer than 5% of the patients with advanced heart failure in the United States are eligible for cardiac transplantation, performed in approximately 2500 patients yearly. Implantable mechanical cardiac support devices have reversed life-threatening hypoperfusion when used as a bridge for patients awaiting transplantation. The recently released results of the Randomized Evaluation of Mechanical Assist Treatment for Congestive Heart failure (REMATCH) trial show that these devices improve survival as destination therapy for patients requiring intravenous inotropic infusions, but serious mechanical, physiologic, and financial limitations remain.

A unique aspect of end-stage heart disease as opposed to other chronic conditions is the availability of implantable cardioverter defibrillators. Although these devices decrease recurrence of life-threatening arrhythmias, the appearance of tachyarrhythmias for some patients heralds a steepening decline of cardiac and clinical function. Increasing hospitalizations for decompensation increase the likelihood of observing nonsustained ventricular tachycardias. Successful defibrillation can prolong the end of life whose quality has diminished to intolerable levels. In the past and in countries where defibrillators are not often implanted, fewer patients survive to suffer from refractory circulatory failure. Before implanting a device that provides a detour at the end of the road, careful reconsideration should be made of the outlook for the journey. Patients should understand the option to deactivate the defibrillation mode.

The appropriate role of inotropic infusions remains unclear. They are often initiated with the expectation that brief support during decompensation will enhance diuresis and accelerate discharge although this assumption has been challenged.35 In some patients, infusions cannot be weaned without clinical deterioration, often with progressive renal dysfunction. Patients are occasionally discharged on these infusions awaiting transplantation. Unfortunately, most patients cannot expect transplantation. Reluctance to confront the impending end of life may lead to the complex prescription of home inotropic infusions, requiring indwelling central catheters with high infection risks, and precious community nursing resources. For most patients truly refractory to other therapies, this approach complicates the end of life while prolonging it by only days or weeks. The expected survival on home inotropic infusions is less than 50% at 3 to 6 months.95,96

Although it is anticipated that programs specializing in advanced heart failure will occasionally maintain outpatients who are receiving continuous inotropic infusions as palliative end-stage care, there is more concern about intermittent inotropic infusions administered 1 to 3 times weekly in outpatients during clinic visits. Improvements described on this therapy have generally been ascribed to the increased frequency of clinical contact.97 Many patients receiving this resource-intensive therapy at one center may be maintained elsewhere on standard oral therapy alone. There are currently no accepted indications for this practice.

Some lessons learned from the care of terminal malignancy can be translated into end-stage heart failure management. As we recognize the elements of discomfort, often perceived as actual pain, and fearfulness during terminal circulatory failure, we are learning to prescribe anxiolytics and narcotics as well as diuretics. When there is alignment of patient and family wishes and community resources, hospice is increasingly used for patients with end-stage heart failure after implantable defibrillators are deactivated.

Horizon for Advanced Heart Failure

The landscape of end-stage heart failure treatment is changing very rapidly, as though viewed from a train. Bases of controlled clinical trial evidence fall far behind the clinical decisions required. Current management as heart failure advances is based more on consensus than on randomized trials. Systematic investigation should address not only new therapies but also strategies for selecting and optimizing therapies already available.

The prolongation of mild to moderate heart failure with ACE inhibitors and β-blockers, and the proliferation of implantable defibrillators have already created a different population of end-stage heart failure, in which right heart failure and renal dysfunction often dominate. Current mechanical support devices offer a limited future but increase expectations of immortality. Careful resource allocation will be required to establish the
appropriate balance between advancing technology for a select population and effective disease management for many.

Even as the end approaches, heart failure is characterized by wide excursion between good and bad days, often preserving hope for another good day until the last. Uncertainty regarding time and mode of death extends that for other terminal illnesses. Even our predictions of imminent death are patches of fog, from which survivors can emerge unexpectedly. Each patient travels a unique journey, on which many share remarkable determination to prevail. As we embolden our patients to understand and influence their course, as we appreciate their individual preferences for quality and length of life, we will guide each other through the changing management of advanced heart failure.

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