

Pharmacotherapy Primer



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Based on the ACC/AHA 2005
Guideline Update

Diagnosis and Management of Chronic Heart Failure in the Adult



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Diagnosis and Management of Chronic Heart Failure in the Adult

Based on the ACC/AHA 2005
Guideline Update

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I. Introduction

This primer is a companion to the ACC/AHA 2005 pocket guidelines for the diagnosis and management of chronic heart failure (HF) in the adult and contains all of the treatment recommendations that are found in the full-text guidelines. It focuses primarily on pharmacological therapy for the treatment of patients with Stage C (current or prior symptoms of HF) and Stage D (refractory end-stage HF), highlighting the caveats and rationales that are found in the full-text guidelines. Information on the treatment of patients at risk for HF but without structural heart disease or symptoms of HF (Stage A), or those with structural heart disease but without signs or symptoms of HF (Stage B), is contained in the full-text guidelines and is not repeated here.

Figure 1. Stages in the Development of Heart Failure/Recommended Therapy by Stage.

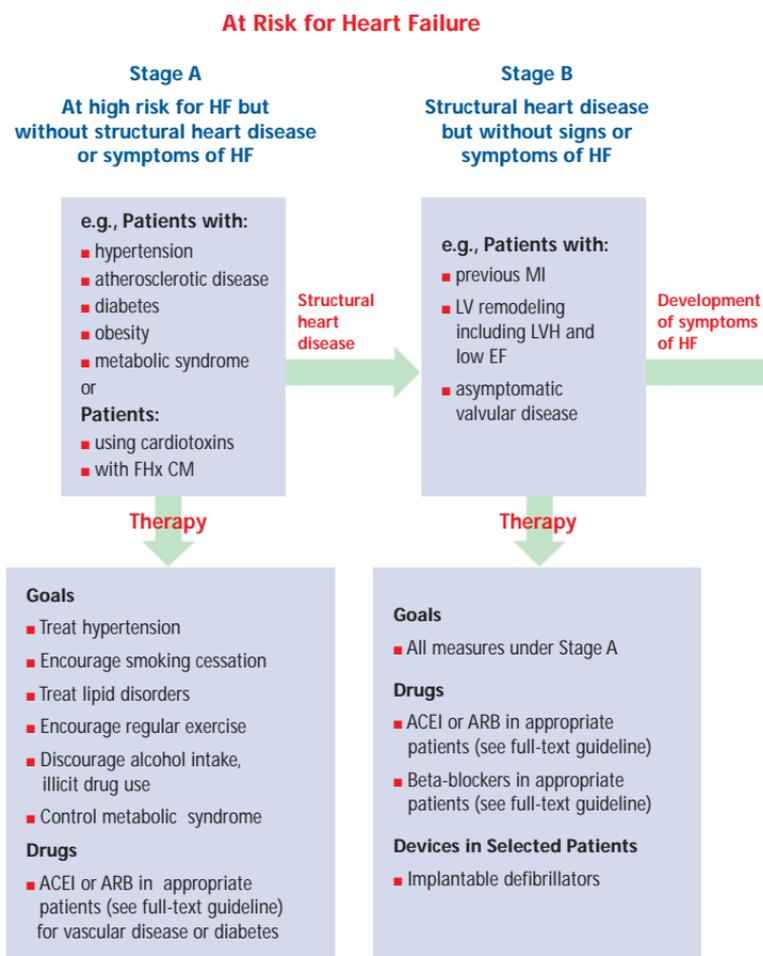
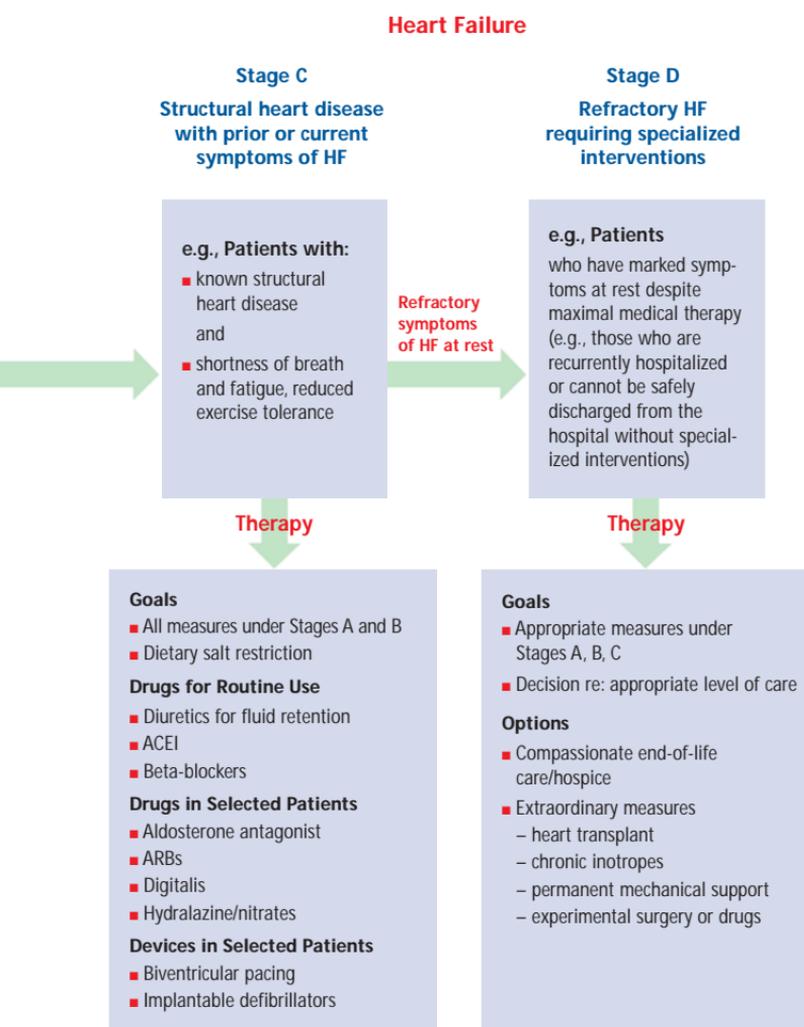


Figure 1 illustrates the stages in the development of HF with recommended therapy associated with each stage. This classification recognizes that there are established risk factors and structural prerequisites for the development of HF and that therapeutic interventions introduced even before the appearance of LV dysfunction or symptoms can reduce the population morbidity and mortality of HF. This classification system is intended to complement but in no way replace the New York Heart Association (NYHA) functional classification, which primarily gauges the severity of symptoms in patients who are in Stage C or Stage D.





II. Therapy

A. Patients With Current or Prior Symptoms of HF (Stage C)

1. Patients With Reduced LVEF

GENERAL MEASURES

Measures listed as class I recommendations for patients in Stages A or B are also appropriate for patients with current or prior symptoms of HF, that is, **hypertension, diabetes mellitus, and lipid abnormalities should be treated according to published guidelines**. In addition, moderate sodium restriction, along with daily measurement of weight, is indicated to permit effective use of lower and safer doses of diuretic drugs, even if overt sodium retention can be controlled by the use of diuretics. Immunization with influenza and pneumococcal vaccines may reduce the risk of a respiratory infection. Although most patients should not participate in heavy labor or exhaustive sports, physical activity should be encouraged (except during periods of acute exacerbation of the signs and symptoms of HF, or in patients with suspected myocarditis), because restriction of activity promotes physical deconditioning, which may adversely affect clinical status and contribute to the exercise intolerance of patients with HF.

Three classes of drugs can exacerbate the syndrome of HF and should be avoided in most patients:

- 1) **Antiarrhythmic agents** can exert important cardiodepressant and proarrhythmic effects. Of available agents, only amiodarone and dofetilide have been shown not to adversely affect survival.
- 2) **Calcium-channel blockers** can lead to worsening HF and have been associated with an increased risk of cardiovascular events. Of available calcium-channel blockers, only the vasoselective ones have been shown not to adversely affect survival.
- 3) **Nonsteroidal anti-inflammatory drugs** can cause sodium retention and peripheral vasoconstriction and can attenuate the efficacy and enhance the toxicity of diuretics and ACEIs. A discussion of the use of aspirin as a unique agent is found later in this section.

Patients with HF should be monitored carefully for changes in serum potassium, and every effort should be made to prevent the occurrence of either hypokalemia or hyperkalemia, both of which may adversely affect cardiac excitability and conduction and may lead to sudden death. Activation of both the sympathetic nervous system and renin-angiotensin systems can lead to hypokalemia, and most drugs used for the treatment of HF can alter serum potassium. Even modest decreases in serum potassium can increase the risks of using digitalis and antiarrhythmic drugs, and even modest increases in serum potassium may prevent the utilization of treatments known

to prolong life. Hence, many experts believe that serum potassium concentrations should be targeted in the 4.0 to 5.0 mmol per liter range. In some patients, correction of potassium deficits may require supplementation of magnesium and potassium. In others (particularly those taking ACEIs alone or in combination with aldosterone antagonists), the routine prescription of potassium salts may be unnecessary and potentially deleterious.

Of the general measures that should be used in patients with HF, possibly the most effective yet least utilized is close attention and follow-up. Nonadherence with diet and medications can rapidly and profoundly affect the clinical status of patients, and increases in body weight and minor changes in symptoms commonly precede by several days the occurrence of major clinical episodes that require emergency care or hospitalization. Patient education and close supervision, which includes surveillance by the patient and his or her family, can reduce the likelihood of nonadherence and lead to the detection of changes in body weight or clinical status early enough to allow the patient or a healthcare provider an opportunity to institute treatments that can prevent clinical deterioration. Supervision need not be performed by a physician and may ideally be accomplished by a nurse or physician assistant with special training in the care of patients with HF. Such an approach has been reported to have significant clinical benefits.

INTERVENTIONS RECOMMENDED FOR ROUTINE USE

Table 1 describes cardiovascular medications useful for treatment of various stages of HF. **Most patients with HF should be routinely managed with a combination of 3 types of drugs: a diuretic, an ACEI or an ARB, and a beta-blocker.** The value of these drugs has been established by the results of numerous large-scale clinical trials, and the evidence supporting a central role for their use is compelling and persuasive. Patients with evidence of fluid retention should take a diuretic until a euvolemic state is achieved, and diuretic therapy should be continued to prevent the recurrence of fluid retention. Even if the patient has responded favorably to the diuretic, treatment with both an ACEI and a beta-blocker should be initiated and maintained in patients who can tolerate them because they have been shown to favorably influence the long-term prognosis of HF. Therapy with digoxin as a fourth agent

Table 1. Cardiovascular Medications Useful for Treatment of Various Stages* of Heart Failure

Drug	Stage C
ACE inhibitors	
Captopril	HF
Enalapril	HF
Fosinopril	HF
Lisinopril	HF
Quinapril	HF
Ramipril	Post MI
Trandolapril	Post MI
Angiotensin receptor blockers	
Candesartan	HF
Valsartan	Post MI, HF
Aldosterone blockers	
Eplerenone	Post MI
Spirolactone	HF
Beta-blockers	
Bisoprolol	HF
Carvedilol	HF, Post MI
Metoprolol succinate	HF
Digoxin	HF

ACE = angiotensin converting enzyme; HF = heart failure; Post MI = reduction in heart failure or other cardiac events following myocardial infarction.

*See Figure 1 for explanation of stages of heart failure.

may be initiated at any time to reduce symptoms, prevent hospitalization, control rhythm, and enhance exercise tolerance.

Diuretics

Diuretics interfere with the sodium retention of HF by inhibiting the reabsorption of sodium or chloride at specific sites in the renal tubules. Bumetanide, furosemide, and torsemide act at the loop of Henle (thus, they are called loop diuretics), whereas thiazides, metolazone, and potassium-sparing agents (e.g., spironolactone) act in the distal portion of the tubule. These 2 classes of diuretics differ in their pharmacological actions. The loop diuretics increase sodium excretion up to 20% to 25% of the filtered load of sodium, enhance free water clearance, and maintain their efficacy unless renal function is severely impaired. In contrast, the thiazide diuretics increase the fractional excretion of sodium to only 5% to 10% of the filtered load, tend to decrease free water clearance, and lose their effectiveness in patients with impaired renal function (creatinine clearance less than 40 mL per min). Consequently, the loop diuretics have emerged as the preferred diuretic agents for use in most patients with HF; however, thiazide diuretics may be preferred in hypertensive HF patients with mild fluid retention because they confer more persistent antihypertensive effects.

Therapy

Patients With
Current or Prior
Symptoms
(Stage C)

Reduced LVEF

Interventions
for Routine Use

Effect of Diuretics in the Management of HF

Controlled trials have demonstrated the ability of diuretic drugs to increase urinary sodium excretion and decrease physical signs of fluid retention in patients with HF. In these short-term studies, diuretic therapy has led to a reduction in jugular venous pressures, pulmonary congestion, peripheral edema, and body weight, all of which were observed within days of initiation of therapy. In intermediate-term studies, diuretics have been shown to improve cardiac function, symptoms, and exercise tolerance in patients with HF. There have been no long-term studies of diuretic therapy in HF, and thus, their effects on morbidity and mortality are not known.

When using diuretics in patients with HF, healthcare providers should keep several points in mind:

- 1) Diuretics produce symptomatic benefits more rapidly than any other drug for HF. They can relieve pulmonary and peripheral edema within hours or days, whereas the clinical effects of digitalis, ACEIs, or beta-blockers may require weeks or months to become apparent.
- 2) Diuretics are the only drugs used for the treatment of HF that can adequately control the fluid retention of HF. Although both digitalis and low doses of ACEIs can enhance urinary sodium excretion, few patients with HF and a history of fluid retention can maintain sodium balance without the use of diuretic drugs. Attempts to substitute ACEIs for diuretics can lead to pulmonary and peripheral congestion.

3) Diuretics should not be used alone in the treatment of Stage C HF. Even when diuretics are successful in controlling symptoms and fluid retention, diuretics alone are unable to maintain the clinical stability of patients with HF for long periods of time. The risk of clinical decompensation can be reduced, however, when diuretics are combined with an ACEI and a beta-blocker.

4) Appropriate use of diuretics is a key element in the success of other drugs used for the treatment of HF. The use of inappropriately low doses of diuretics will result in fluid retention, which can diminish the response to ACEIs and increase the risk of treatment with beta-blockers. Conversely, the use of inappropriately high doses of diuretics will lead to volume contraction, which can increase the risk of hypotension with ACEIs and vasodilators and the risk of renal insufficiency with ACEIs and ARBs. Optimal use of diuretics is the cornerstone of any successful approach to the treatment of HF.

Practical Use of Diuretic Therapy

Selection of patients

Diuretics should be prescribed to all patients who have evidence of, and to most patients with a prior history of, fluid retention. Diuretics should generally be combined with an ACEI and a beta-blocker. Few patients with HF will be able to maintain dry weight without the use of diuretics. Oral diuretics recommended for use in the treatment of chronic HF are shown in Table 2. Intravenous diuretic medications useful for the treatment of severe HF are listed in Table 3.

Table 2. Oral Diuretics Recommended for Use in the Treatment of Chronic Heart Failure

Drug	Initial Daily Dose(s)	Maximum Total Daily Dose	Duration of Action
Loop diuretics			
Bumetanide	0.5 to 1.0 mg once or twice	10 mg	4 to 6 hours
Furosemide	20 to 40 mg once or twice	600 mg	6 to 8 hours
Torsemide	10 to 20 mg once	200 mg	12 to 16 hours
Thiazide diuretics			
Chlorothiazide	250 to 500 mg once or twice	1000 mg	6 to 12 hours
Chlorthalidone	12.5 to 25 mg once	100 mg	24 to 72 hours
Hydrochlorothiazide	25 mg once or twice	200 mg	6 to 12 hours
Indapamide	2.5 once	5 mg	36 hours
Metolazone	2.5 mg once	20 mg	12 to 24 hours
Potassium-sparing diuretics[†]			
Amiloride	5 mg once	20 mg	24 hours
Spirolactone	12.5 to 25 mg once	50 mg*	2 to 3 days
Triamterene	50 to 75 mg twice	200 mg	7 to 9 hours
Sequential nephron blockade			
Metolazone	2.5 to 10 mg once plus loop diuretic	–	–
Hydrochlorothiazide	25 to 100 mg once or twice plus loop diuretic	–	–
Chlorothiazide (IV)	500 to 1000 mg once plus loop diuretic	–	–

mg = milligrams; IV = intravenous.

*Higher doses may occasionally be used with close monitoring.

[†]Eplerenone, although also a diuretic, is primarily used in chronic heart failure as a suppressor of the renin-angiotensin-aldosterone system.

Table 3. Intravenous Diuretic Medications Useful for the Treatment of Severe Heart Failure

Drug	Initial Dose	Maximum Single Dose
Loop diuretics		
Bumetanide	1.0 mg	4 to 8 mg
Furosemide	40 mg	160 to 200 mg
Torsemide	10 mg	100 to 200 mg
Thiazide diuretics		
Chlorothiazide	500 mg	1000 mg
Sequential nephron blockade		
	Chlorothiazide 500 to 1000 mg IV once or twice plus loop diuretics once; multiple doses per day	
	Metolazone (as Zaroxolyn or Diulo) 2.5 to 5 mg PO once or twice daily with loop diuretic	
Intravenous infusions		
Bumetanide	1-mg IV load, then 0.5 to 2 mg per hour infusion	
Furosemide	40-mg IV load, then 10 to 40 mg per hour infusion	
Torsemide	20-mg IV load, then 5 to 20 mg per hour infusion	

mg = milligrams; IV = intravenous; PO = by mouth.

Initiation and maintenance

The most commonly used loop diuretic for the treatment of HF is furosemide, but some patients respond favorably to other agents in this category (such as torsemide) because of superior absorption and longer duration of action. In outpatients with HF, therapy is commonly initiated with low doses of a diuretic, and the dose is increased until urine output increases and weight decreases, generally by 0.5 to 1.0 kg daily. Further increases in the dose or frequency (i.e., twice-daily dosing) of diuretic administration may be required to maintain an active diuresis and sustain the loss of weight. The ultimate goal of diuretic treatment is to eliminate clinical evidence of fluid retention, such as jugular venous pressure elevation and peripheral edema. Diuretics are generally combined with moderate dietary sodium restriction (3 to 4 g daily).

If electrolyte imbalances are seen, these should be treated aggressively and the diuresis continued. If hypotension or azotemia is observed before the goals of treatment are achieved, the physician may elect to slow the rapidity of diuresis, but diuresis should nevertheless be maintained until fluid retention is eliminated, even if this strategy results in mild or moderate decreases in blood pressure or renal function, as long as the patient remains asymptomatic. Excessive concern about hypotension and azotemia can lead to the underutilization of diuretics and a state of refractory edema.

Therapy

Patients With Current or Prior Symptoms (Stage C)

Reduced LVEF

Interventions for Routine Use

Persistent volume overload not only contributes to the persistence of symptoms but may also limit the efficacy and compromise the safety of other drugs used for the treatment of HF.

Once fluid retention has resolved, treatment with the diuretic should be maintained to prevent the recurrence of volume overload. Patients are commonly prescribed a fixed dose of diuretic, but the dose of these drugs frequently may need adjustment. In many cases, this adjustment can be accomplished by having patients record their weight each day and make changes in their diuretic dosage if the weight increases or decreases beyond a specified range.

The response to a diuretic is dependent on the concentration of the drug and the time course of its entry into the urine. Patients with mild HF respond favorably to low doses because they absorb diuretics rapidly from the bowel and deliver these drugs rapidly to the renal tubules. However, as HF advances, the absorption of the drug may be delayed by bowel edema or intestinal hypoperfusion, and the delivery of the drug and the response to a given intratubular concentration may be impaired by a decline in renal perfusion and function. Consequently, the clinical progression of HF is characterized by the need for increasing doses of diuretics.

Patients may become unresponsive to high doses of diuretic drugs if they consume large amounts of dietary sodium, are taking agents that can block the effects of diuretics (e.g., nonsteroidal anti-inflammatory drugs, including cyclo-oxygenase-2 inhibitors), or have a significant impairment of renal function or perfusion. Diuretic resistance can generally be overcome by the intravenous administration of diuretics (including the use of continuous infusions), the use of 2 or more diuretics in combination (e.g., furosemide and metolazone), or the use of diuretics together with drugs that increase renal blood flow (e.g., positive inotropic agents).

Risks of treatment

The principal adverse effects of diuretics include electrolyte and fluid depletion, as well as hypotension and azotemia. Diuretics may also cause rashes and hearing difficulties, but these are generally idiosyncratic or are seen with the use of very large doses, respectively.

Diuretics can cause the depletion of important cations (potassium and magnesium), which can predispose patients to serious cardiac arrhythmias, particularly in the presence of digitalis therapy. The risk of electrolyte depletion is markedly enhanced when 2 diuretics are used in combination. The loss of electrolytes is related to enhanced delivery of sodium to distal sites in the renal tubules and the exchange of sodium for other cations, a process that is potentiated by activation of the renin-angiotensin-aldosterone system. Potassium deficits can be corrected by the short-term use of potassium supplements or, if severe, by the addition of magnesium supplements. Concomitant administration of ACEIs alone or in combination with potassium-retaining agents (such as spironolactone) can prevent electrolyte depletion in most patients with HF who are taking a loop diuretic. When these drugs are prescribed, long-term oral potassium supplementation frequently is not needed and may be deleterious.

Excessive use of diuretics can decrease blood pressure and impair renal function and exercise tolerance, but hypotension and azotemia may also occur as a result of worsening HF, which may be exacerbated by attempts to reduce the dose of diuretics. If there are no signs of fluid retention, hypotension and azotemia are likely to be related to volume depletion and may resolve after a reduction in diuretic dose. **The signs of fluid retention, hypotension and azotemia, are likely to reflect worsening HF and a decline in effective peripheral perfusion.** This is an ominous clinical scenario and necessitates considering the measures discussed under Stage D HF.

Inhibitors of the Renin-Angiotensin-Aldosterone System

Inhibition of the renin-angiotensin-aldosterone system can take place at multiple sites: at the level of the enzyme that converts angiotensin I to angiotensin II (ACEIs), at the angiotensin receptor (ARBs), or at the receptor for aldosterone, which is under control of both the renin-angiotensin system and other systemic and local influences (aldosterone antagonists). Angiotensin converting enzyme inhibitors are the best studied class of agents in HF, with multiple mechanisms of benefit for both HF, coronary disease, and other atherosclerotic vascular disease, as well as diabetic nephropathy. During chronic therapy with ACEIs, the renin-angiotensin system demonstrates partial “escape” from inhibition with “normalization” of angiotensin levels, in part owing to alternative local pathways for production of angiotensin. This leaves the potential for benefit from additional therapy with ARBs and with the aldosterone antagonists.

Angiotensin Converting Enzyme Inhibitors

Angiotensin Converting Enzyme Inhibitors in the Management of HF

It is not clear whether the effects of ACEIs can be explained solely by the suppression of angiotensin II production, because ACE inhibition not only interferes with the renin-angiotensin system but also enhances the action of kinins and augments kinin-mediated prostaglandin production. In experimental models of HF, ACEIs modify cardiac remodeling more favorably than ARBs, and this advantage of ACEIs is abolished by the coadministration of a kinin receptor blocker. Angiotensin converting enzyme inhibitors have been evaluated in more than 7,000 patients with HF who participated in more than 30 placebo-controlled clinical trials. All of these trials enrolled patients with reduced LVEF (EF less than 35% to 40%) who were treated with diuretics, with or without digitalis. These trials recruited many types of patients, including women and the elderly, as well as patients with a wide range of causes and severity of LV dysfunction. However, patients with preserved systolic function, low blood pressure (less

Therapy

Patients With
Current or Prior
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(Stage C)

Reduced LVEF

Interventions
for Routine Use

than 90 mm Hg systolic), or impaired renal function (serum creatinine greater than 2.5 mg per mL) were not recruited or represented a small proportion of patients who participated in these studies.

Analysis of this collective experience indicates that ACEIs can alleviate symptoms, improve clinical status, and enhance the overall sense of well-being of patients with HF. In addition, ACEIs can reduce the risk of death and the combined risk of death or hospitalization. These benefits of ACE inhibition were seen in patients with mild, moderate, or severe symptoms and in patients with or without coronary artery disease.

Practical Use of ACE Inhibitors

Selection of patients

Angiotensin converting enzyme inhibitors should be prescribed to all patients with HF due to reduced LVEF unless they have a contraindication to their use or have been shown to be unable to tolerate treatment with these drugs. Because of their favorable effects on survival, treatment with an ACEI should not be delayed until the patient is found to be resistant to treatment with other drugs.

In general, ACEIs are used together with a beta-blocker. Angiotensin converting enzyme inhibitors should not be prescribed without diuretics in patients with a current or recent history of fluid retention, because diuretics are needed to maintain sodium balance and prevent the development of peripheral and pulmonary edema. Angiotensin converting enzyme inhibitors are often preferred over ARBs or direct-acting vasodilators because of the greater experience and weight of evidence in support of their effectiveness.

Patients should not be given an ACEI if they have experienced life-threatening adverse reactions (angioedema or anuric renal failure) during previous exposure to the drug or if they are pregnant. They should take an ACEI with caution if they have very low systemic blood pressures (systolic blood pressure less than 80 mm Hg), markedly increased serum levels of creatinine (greater than 3 mg per dL), bilateral renal artery stenosis, or elevated levels of serum potassium (greater than 5.5 mmol per liter). Finally, treatment with an ACEI should not be initiated in hypotensive patients who are at immediate risk of cardiogenic shock. Such patients should first receive other forms of treatment for their HF and then be re-evaluated for ACE inhibition once stability has been achieved.

Initiation and maintenance

Although most of the evidence that supports an effect of ACEIs on the survival of patients with HF is derived from experience with enalapril, the available data suggest that there are no differences among available ACEIs in their effects on symptoms or survival. Although some have suggested that drugs in this class may differ in their ability to inhibit tissue ACE, no trial has shown that tissue ACE-inhibiting agents are superior to other ACEIs in any clinical



aspect of HF. Nevertheless, in selecting among ACEIs, it is recommended that preference be given to ACEIs that have been shown to reduce morbidity and mortality in clinical trials in HF or post-MI populations (captopril, enalapril, lisinopril, perindopril, ramipril, and trandolapril), because these studies have clearly defined a dose that is effective in modifying the natural history of the disease. Such information is generally lacking for ACEIs that have not been shown to be effective in large-scale studies.

Treatment with an ACEI should be initiated at low doses (see Table 4), followed by gradual increments in dose if lower doses have been well tolerated. Renal function and serum potassium should be assessed within 1 to 2 weeks of initiation of therapy and periodically thereafter, especially in patients with pre-existing hypotension, hyponatremia, diabetes mellitus, or azotemia or in those taking

Therapy

Patients With
Current or Prior
Symptoms
(Stage C)

Reduced LVEF

Interventions
for Routine Use

Table 4. Inhibitors of the Renin-Angiotensin-Aldosterone System and Beta-Blockers Commonly Used for the Treatment of Patients With Heart Failure With Low Ejection Fraction

Drug	Initial Daily Dose(s)	Maximum Dose(s)
ACE inhibitors		
Captopril	6.25 mg 3 times	50 mg 3 times
Enalapril	2.5 mg twice	10 to 20 mg twice
Fosinopril	5 to 10 mg once	40 mg once
Lisinopril	2.5 to 5 mg once	20 to 40 mg once
Perindopril	2 mg once	8 to 16 mg once
Quinapril	5 mg twice	20 mg twice
Ramipril	1.25 to 2.5 mg once	10 mg once
Trandolapril	1 mg once	4 mg once
Angiotensin receptor blockers		
Candesartan	4 to 8 mg once	32 mg once
Losartan	25 to 50 mg once	50 to 100 mg once
Valsartan	20 to 40 mg twice	160 mg twice
Aldosterone antagonists		
Spirolonactone	12.5 to 25 mg once	25 mg once or twice
Eplerenone	25 mg once	50 mg once
Beta-blockers		
Bisoprolol	1.25 mg once	10 mg once
Carvedilol	3.125 mg twice	25 mg twice 50 mg twice for patients > 85 kg
Metoprolol succinate extended release (metoprolol CR/XL)	12.5 to 25 mg once	200 mg once

ACE = angiotensin converting enzyme; mg = milligrams; kg = kilograms.

potassium supplements. Because fluid retention can blunt the therapeutic effects and fluid depletion can potentiate the adverse effects of ACE, healthcare providers should ensure that patients are being given appropriate doses of diuretics before and during treatment with these drugs. **Most patients (85% to 90%) with HF can tolerate short- and long-term therapy with these drugs.**

What dose of an ACEI should physicians try to achieve in patients with HF? In controlled clinical trials that were designed to evaluate survival, the dose of the ACEI was not determined by a patient's therapeutic response but was increased until a target dose was reached. However, these drugs are commonly prescribed in clinical practice at much lower doses that are similar to those recommended for initiation rather than maintenance of therapy. Which approach should be followed? In the controlled clinical trials of ACEIs, low or intermediate doses were commonly prescribed if higher doses could not be tolerated. In controlled trials with newer agents for HF, intermediate doses rather than high doses of ACEIs were generally used as background therapy. Higher doses of an ACEI were better than low doses in reducing the risk of hospitalization, but they showed similar effects on symptoms and mortality. Clinicians should attempt to use doses that have been shown to reduce the risk of cardiovascular events in clinical trials. If these target doses of an ACEI cannot be used or are poorly tolerated, intermediate doses should be used with the expectation that there are likely to be only small differences in efficacy between low and high doses. More importantly, **clinicians should not delay the institution of beta-blockers in patients because of a failure to reach target ACEI doses.** Once the drug has been titrated to the appropriate dose, patients can generally be maintained on long-term therapy with an ACEI with little difficulty. Although symptoms may improve in some patients within the first 48 hours of therapy with an ACEI, the clinical responses to these drugs are generally delayed and may require several weeks, months, or more to become apparent. Even if symptoms do not improve, long-term treatment with an ACEI should be maintained to reduce the risk of death or hospitalization. Abrupt withdrawal of treatment with an ACEI can lead to clinical deterioration and should be avoided in the absence of life-threatening complications (e.g., angioedema).

Every effort should be made to minimize the occurrence of sodium retention or depletion during long-term treatment with an ACEI, because changes in salt and water balance can exaggerate or attenuate the cardiovascular and renal effects of treatment. Fluid retention can minimize the symptomatic benefits of ACE inhibition, whereas fluid loss increases the risk of hypotension and azotemia. The use of an ACEI can also minimize or eliminate the need for long-term potassium supplementation. **Nonsteroidal anti-inflammatory drugs can block the favorable effects and enhance the adverse effects of ACEIs in patients with HF and should be avoided.**

Therapy

Patients With
Current or Prior
Symptoms
(Stage C)

Reduced LVEF

Interventions
for Routine Use

Clinical experience in patients who are hemodynamically or clinically unstable suggests that the hypotensive effects of ACE inhibition may attenuate the natriuretic response to diuretics and antagonize the pressor response to intravenous vasoconstrictors. As a result, in such patients (particularly those who are responding poorly to diuretic drugs), it may be prudent to interrupt treatment with the ACEI temporarily until the clinical status of the patient stabilizes.

Retrospective analyses of large-scale clinical trials have suggested that aspirin might interfere with the benefits of ACE inhibition in patients with HF by inhibiting kinin-mediated prostaglandin synthesis. In short-term hemodynamic and maximal-exercise studies, aspirin can attenuate the hemodynamic actions of ACEIs in patients with HF, an effect not seen with nonaspirin antiplatelet agents (e.g., clopidogrel).

In several multicenter trials, concomitant use of aspirin was associated with a diminution of the effect of ACEIs on survival and on cardiovascular morbidity. A recent comprehensive systematic overview of 22 060 patients from 6 long-term randomized trials of ACEIs re-evaluated the issue of the potential detrimental effect of combining aspirin with ACEI therapy. When all of these trials were considered together, **the effects of ACEIs were significantly beneficial in patients with and without aspirin therapy.** The composite risk reduction was 20% for patients taking aspirin and 29% for those not taking aspirin, a difference that did not reach statistical significance. A second retrospective review subsequently also reported no adverse effect of concomitant aspirin use with ACEIs on long-term survival. Given these retrospective results, many physicians believe the data justify prescribing aspirin and ACEIs together when there is an indication for use of aspirin. However, these large overviews are subject to varying interpretation. Other physicians would consider not combining aspirin with an ACEI because there are no data to indicate that it can reduce the risk of ischemic events in patients with HF, or they might consider the use of an alternative antiplatelet agent such as clopidogrel, which does not interact with ACEIs and which may have superior effects in preventing ischemic events. However, clopidogrel does not have an indication for the primary prevention of ischemic events. **There may be an important interaction between aspirin and ACEIs, but there is controversy regarding this point, and it requires further study.**

Risks of treatment

Most of the adverse reactions of ACEIs can be attributed to the 2 principal pharmacological actions of these drugs: those related to angiotensin suppression and those related to kinin potentiation. Other types of side effects may also occur (e.g., rash and taste disturbances).

Adverse effects related to angiotensin suppression

1. Hypotension. The most common adverse effects of ACE inhibition in patients with HF are hypotension and dizziness. Blood pressure declines without symptoms in nearly every patient treated with an ACEI, so hypotension is generally a concern only if it is accompanied by postural symptoms, worsening renal function, blurred vision, or syncope. Hypotension is seen most frequently during the first few days of initiation of increments in therapy, particularly in patients with hypovolemia, a recent marked diuresis, or severe hyponatremia (serum sodium concentration less than 130 mmol per liter).

Should symptomatic hypotension occur with the first doses, it may not recur with repeated administration of the same doses of the drug. However, it is prudent under such circumstances to reduce the activation of and dependence on the renin-angiotensin system by reducing the dose of diuretics, liberalizing salt intake, or both, provided the patient does not have significant fluid retention. The doses of other hypotensive agents (especially vasodilators) can be reduced or staggered so their peak effect does not coincide with that of the ACEI. Most patients who experience early symptomatic hypotension remain excellent candidates for long-term ACE inhibition if appropriate measures are taken to minimize recurrent hypotensive reactions.

2. Worsening renal function. In states characterized by reduced renal perfusion (such as HF), glomerular filtration is critically dependent on angiotensin-mediated efferent arteriolar vasoconstriction, and ACE inhibition may cause functional renal insufficiency. Because the decline in glomerular filtration is related to the withdrawal of the actions of angiotensin II, the risk of azotemia is highest in patients who are most dependent on the renin-angiotensin system for support of renal homeostasis (i.e., class IV or hyponatremic patients).

A significant increase in serum creatinine (e.g., greater than 0.3 mg per dL) with the use of ACEIs is observed in 15% to 30% of patients with severe HF, but in only 5% to 15% of patients with mild to moderate symptoms. The risks are substantially greater if patients have bilateral renal artery stenosis or are taking nonsteroidal anti-inflammatory drugs. Renal function usually improves after a reduction in the dose of concomitantly administered diuretics, and thus, these patients can generally be managed without the need to withdraw treatment with the ACEI. However, if the dose of diuretic cannot be reduced because the patient has fluid retention, the physician and patient may need to tolerate mild to moderate degrees of azotemia to maintain therapy with the ACEI.



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3. Potassium retention. Hyperkalemia can occur during ACE inhibition in patients with HF and may be sufficiently severe to cause cardiac conduction disturbances. In general, hyperkalemia is seen in patients whose renal function deteriorates or who are taking oral potassium supplements or potassium-sparing diuretics, or aldosterone antagonists, especially if they have diabetes mellitus.

Adverse effects related to kinin potentiation

1. Cough. Cough related to the use of ACEIs is the most common reason for the withdrawal of long-term treatment with these drugs; the frequency of cough is approximately 5% to 10% in white patients of European descent and rises to nearly 50% in Chinese patients. It is characteristically nonproductive, is accompanied by a persistent and annoying “tickle” in the back of the throat, usually appears within the first months of therapy, disappears within 1 to 2 weeks of discontinuing treatment, and recurs within days of rechallenge. Other causes of cough, especially pulmonary congestion, should always be considered, and the ACEI should be implicated only after these have been excluded. Demonstration that the cough disappears after drug withdrawal and recurs after rechallenge with another ACEI strongly suggests that ACE inhibition is the cause of the cough. In a number of studies of ACEI cough, it was found that this symptom did not recur with rechallenge and probably was a coincidental finding. Because of the long-term benefits of ACEIs, physicians should encourage patients to continue taking these drugs if the cough is not severe. Only if the cough proves to be persistent and troublesome should the physician consider withdrawal of the ACEI and the use of alternative medications (e.g., an ARB).

2. Angioedema. Angioedema occurs in fewer than 1% of patients taking an ACEI but is more frequent in black patients. Because its occurrence may be life-threatening, the clinical suspicion of this reaction justifies subsequent avoidance of all ACEIs for the lifetime of the patient. Angiotensin converting enzyme inhibitors should not be initiated in any patient with a history of angioedema. Although ARBs may be considered as alternative therapy for patients who have developed angioedema while taking an ACEI, there are a number of patients who have also developed angioedema with ARBs, and extreme caution is advised when substituting an ARB in a patient who has had angioedema associated with ACEI use.

Angiotensin Receptor Blockers

Agents that block these receptors were developed on the rationale that 1) angiotensin II production continues in the presence of ACE inhibition, driven through alternative enzyme pathways, and 2) interference with the renin-angiotensin system without inhibition of kininase would produce all of the benefits of ACEIs while minimizing the risk of their adverse reactions. However, it is now known that

some of the benefits may be related to the accumulation of kinins rather than to the suppression of angiotensin II formation, whereas some of the side effects of ACEIs in HF are related to the suppression of angiotensin II formation.

Several ARBs (e.g., candesartan, eprosartan, irbesartan, losartan, telmisartan, olmesartan, valsartan) are available for clinical use. Experience with these drugs in controlled clinical trials of patients with HF is considerably less than that with ACEIs. Nevertheless, in several placebo-controlled studies, long-term therapy with ARBs produced hemodynamic, neurohormonal, and clinical effects consistent with those expected after interference with the renin-angiotensin system. In patients with evidence of LV dysfunction early after MI, a recent trial demonstrated that ARBs had a benefit that was not inferior to that of ACEIs without an advantage in terms of tolerability. However, the addition of an ARB to an ACEI did not improve outcomes and resulted in more side effects.

For patients unable to tolerate ACEIs because of cough or angioedema, the ARBs valsartan and candesartan have demonstrated benefit by reducing hospitalizations and mortality. The combination of an ACEI and ARBs may produce more reduction of LV size than either agent alone. The addition of ARBs to chronic ACEI therapy caused a modest decrease in hospitalization in 2 studies, with a trend to decreased total mortality in one and no impact on mortality in another.

Recommendations Concerning ARBs

Angiotensin converting enzyme inhibitors remain the first choice for inhibition of the renin-angiotensin system in chronic HF, but ARBs can now be considered a reasonable alternative. Candesartan improved outcomes in patients with preserved LVEF who were intolerant of ACEIs in the Candesartan in Heart Failure Assessment of Reduction in Mortality and Morbidity (CHARM)-Alternative trial. Angiotensin receptor blockers are as likely to produce hypotension, worsening renal function, and hyperkalemia as ACEIs. Although angioedema is much less frequent with ARBs, there are cases of patients who developed angioedema to both ACEIs and later to ARBs. There is little information available about the addition of ARBs to therapy with both ACEIs and aldosterone antagonists, but risks of renal dysfunction and hyperkalemia would be further increased. Until further information is available, the routine combined use of all 3 inhibitors of the renin-angiotensin system cannot be recommended.

Practical Use of ARBs

Initiation and maintenance. When used, angiotensin receptor blockers should be initiated with the starting doses shown in Table 4. Many of the considerations with ARBs are similar to those with initiation of an ACEI, as discussed above. Blood pressure (including postural blood pressure changes), renal function, and

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potassium should be reassessed within 1 to 2 weeks after initiation and followed closely after changes in dose. Patients with systolic blood pressure below 80 mm Hg, low serum sodium, diabetes mellitus, and impaired renal function merit particular surveillance during therapy with inhibitors of the renin-angiotensin-aldosterone system. Titration is generally achieved by doubling doses. For stable patients, it is reasonable to add therapy with beta-blocking agents before full target doses of either ACEIs or ARBs are reached.

The risks of treatment with ARBs are those attributed to suppression of angiotensin stimulation, as discussed above for ACEIs. These risks of hypotension, renal dysfunction, and hyperkalemia are greater when combined with another inhibitor of this axis, such as ACEIs or aldosterone antagonists.

Aldosterone Antagonists

Although short-term therapy with both ACEIs and ARBs can lower circulating levels of aldosterone, such suppression may not be sustained during long-term treatment. The lack of long-term suppression may be important, because experimental data suggest that aldosterone exerts adverse effects on the structure and function of the heart independently of and in addition to the deleterious effects produced by angiotensin II.

Spirolactone is the most widely used aldosterone antagonist. In a large-scale long-term trial, low doses of spironolactone (starting at 12.5 mg daily) were added to ACEI therapy for patients with NYHA class IV HF symptoms or class III symptoms and recent hospitalization. The risk of death was reduced from 46% to 35% (30% relative risk reduction) over 2 years, with a 35% reduction in HF hospitalization and an improvement in functional class. Initial creatinine levels were below 2.0 mg per dL in the dose-ranging pilot trial and below 2.5 mg per dL in the main trial. Potassium replacements were stopped at trial entry, and serum potassium and renal function were followed very closely.

A trial investigated the newer aldosterone antagonist eplerenone in patients with LVEF less than or equal to 40% and clinical evidence of HF or diabetes mellitus within 14 days of MI. Mortality was decreased from 13.6% to 11.8% at 1 year. Hyperkalemia occurred in 5.5% of patients treated with eplerenone compared with 3.9% of those given placebo overall and in up to 10.1% versus 4.6% of patients with estimated creatinine clearance less than 50 mL per min.

Recommendations Concerning Aldosterone Antagonists

The addition of low-dose aldosterone antagonists should be considered in carefully selected patients with moderately severe or severe HF symptoms and recent decompensation or with LV dysfunction early after MI. These recommendations are based on the strong data

demonstrating reduced death and rehospitalization in 2 clinical trial populations. The entry criteria for these trials describe a broader population than was actually enrolled, such that the favorable efficacy/toxicity ratio may not be as applicable to patients at the margins of trial eligibility. For both of these major trials, patients were excluded for a serum creatinine level in excess of 2.5 mg per dL, but few patients were actually enrolled with serum creatinine levels over 1.5 mg per dL. In the trial of patients after MI, there was a significant interaction between serum creatinine and benefit of eplerenone. The average serum creatinine of enrolled patients was 1.1 mg per dL, above which there was no demonstrable benefit for survival.

To minimize the risk of life-threatening hyperkalemia in patients with low LVEF and symptoms of HF, patients should have initial serum creatinine less than 2.0 to 2.5 mg per dL without recent worsening and serum potassium less than 5.0 mEq per dL without a history of severe hyperkalemia. In view of the consistency of evidence for patients with low LVEF early after MI and patients with recent decompensation and severe symptoms, it may be reasonable to consider addition of aldosterone antagonists to loop diuretics for some patients with mild to moderate symptoms of HF; however, the Writing Committee strongly believes that there are insufficient data or experience to provide a specific or strong recommendation. Because the safety and efficacy of aldosterone antagonist therapy has not been shown in the absence of loop diuretic therapy, it is not currently recommended that such therapy be given without other concomitant diuretic therapy in chronic HF. **Although 17% of patients in the CHARM add-on trial were receiving spironolactone, the safety of the combination of ACEIs, ARBs, and aldosterone antagonists has not been explored adequately, and this combination cannot be recommended.**



Practical Use of Aldosterone Antagonists

Selection of patients. Decisions regarding the selection of patients for aldosterone antagonists reflect the balance between potential benefit to decrease death and hospitalization from HF and potential risks of life-threatening hyperkalemia. Despite this, patients who meet recommended criteria from formal trials may need to be excluded in practice for a recent history of renal dysfunction characterized by higher creatinine, markedly elevated blood urea nitrogen, or hyperkalemia, particularly in the presence of insulin-requiring diabetes mellitus. Serum creatinine levels often underestimate renal dysfunction, particularly in the elderly, in whom estimated creatinine clearance less than 50 mL per min should trigger a reduction of the initial dose of spironolactone to 12.5 mg daily or of eplerenone to

25 mg daily, and aldosterone antagonists should not be given when clearance is less than 30 mL per min (see Table 5). Patients chronically requiring high doses of diuretics without potassium replacement should be evaluated closely, because potassium handling may be impaired.

Risks of Aldosterone Antagonists

The major risk of aldosterone antagonists is hyperkalemia due to inhibition of potassium excretion. Renal dysfunction may be aggravated, which further impairs potassium excretion. Although aldosterone antagonists usually have a relatively weak diuretic effect, some patients may experience marked potentiation of other diuretic therapy after the addition of aldosterone antagonists. Fluid depletion can occur, which further increases the risk of renal dysfunction and hyperkalemia. During chronic therapy after initial stabilization, hyperkalemia may occur in the setting of other conditions that cause volume depletion, such as gastroenteritis. Gynecomastia or other antiandrogen effects that can occur during therapy with spironolactone are not generally seen with the newer aldosterone antagonist eplerenone.

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Table 5. Guidelines for Minimizing the Risk of Hyperkalemia in Patients Treated With Aldosterone Antagonists

1. Impaired renal function is a risk factor for hyperkalemia during treatment with aldosterone antagonists. The risk of hyperkalemia increases progressively when serum creatinine exceeds 1.6 mg per dL.* In elderly patients or others with low muscle mass in whom serum creatinine does not accurately reflect glomerular filtration rate, determination that glomerular filtration rate or creatinine clearance exceeds 30 mL per min is recommended.
2. Aldosterone antagonists should not be administered to patients with baseline serum potassium in excess of 5.0 mEq per liter.
3. An initial dose of spironolactone 12.5 mg or eplerenone 25 mg is recommended, after which the dose may be increased to spironolactone 25 mg or eplerenone 50 mg if appropriate.
4. The risk of hyperkalemia is increased with concomitant use of higher doses of ACE inhibitors (captopril greater than or equal to 75 mg daily; enalapril or lisinopril greater than or equal to 10 mg daily).
5. Non-steroidal anti-inflammatory drugs and cyclo-oxygenase-2 inhibitors should be avoided.
6. Potassium supplements should be discontinued or reduced.
7. Close monitoring of serum potassium is required; potassium levels and renal function should be checked in 3 days and at 1 week after initiation of therapy and at least monthly for the first 3 months.
8. Diarrhea or other causes of dehydration should be addressed emergently.

ACE = angiotensin converting enzyme.

*Although the entry criteria for the trials of aldosterone antagonists included creatinine greater than 2.5 mg per dL, the majority of patients had creatinine much lower; in 1 trial, 95% of patients had creatinine less than or equal to 1.7 mg per dL.

Initiation and Monitoring. Spironolactone should be initiated at a dose of 12.5 to 25 mg daily, or occasionally on alternate days. Eplerenone was used after MI in one study at doses of 25 mg per d, increasing to 50 mg daily. Potassium supplementation is generally stopped after the initiation of aldosterone antagonists, and patients should be counseled to avoid high potassium-containing foods. However, patients who have required large amounts of potassium supplementation may need to continue receiving supplementation, albeit at a lower dose, particularly when previous episodes of hypokalemia have been associated with ventricular arrhythmias. On the other hand, potassium supplementation required during vigorous therapy of fluid overload is often no longer necessary once the goal is to maintain even fluid balance. Patients should be cautioned to avoid the addition of nonsteroidal anti-inflammatory agents and cyclo-oxygenase-2 inhibitors, which can lead to worsening renal function and hyperkalemia. Potassium levels and renal function should be rechecked within 3 days and again at 1 week after initiation of an aldosterone antagonist. Subsequent monitoring should be dictated by the general clinical stability of renal function and fluid status but should occur at least monthly for the first 3 months and every 3 months thereafter. The addition or an increase in dosage of ACEIs or ARBs should trigger a new cycle of monitoring. In view of the potential risk for hyperkalemia, the Writing Committee recommends that the routine triple combination of ACEIs, ARBs, and an aldosterone antagonist be avoided.

The development of potassium levels in excess of 5.5 mEq per liter should generally trigger discontinuation or dose reduction of the aldosterone antagonist unless patients have been receiving potassium supplementation, which should then be stopped. The development of worsening renal function should lead to careful evaluation of the entire medical regimen and consideration for stopping the aldosterone antagonist. Patients should be instructed specifically to stop the aldosterone antagonist during an episode of diarrhea or while loop diuretic therapy is interrupted.

Beta-Adrenergic Receptor Blockers

Beta-blockers act principally to inhibit the adverse effects of the sympathetic nervous system in patients with HF, and these effects far outweigh their well-known negative inotropic effects. Whereas cardiac adrenergic drive initially supports the performance of the failing heart, long-term activation of the sympathetic nervous system exerts deleterious effects that can be antagonized by the use of beta-blockers. Sympathetic activation can increase ventricular volumes and pressure by causing peripheral vasoconstriction and by impairing sodium excretion by the kidneys. Norepinephrine can also induce cardiac hypertrophy but restrict the ability of the coronary arteries to

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supply blood to the thickened ventricular wall, leading to myocardial ischemia. Activation of the sympathetic nervous system can also provoke arrhythmias by increasing the automaticity of cardiac cells, increasing triggered activity in the heart, and promoting the development of hypokalemia. Norepinephrine can also increase heart rate and potentiate the activity and actions of other neurohormonal systems. Finally, by stimulating growth and oxidative stress in terminally differentiated cells, norepinephrine can trigger programmed cell death or apoptosis. These deleterious effects are mediated through actions on alpha-1-, beta-1-, and beta-2-adrenergic receptors.

Three beta-blockers have been shown to be effective in reducing the risk of death in patients with chronic HF: bisoprolol and sustained-release metoprolol (succinate), which selectively block beta-1-receptors, and carvedilol, which blocks alpha-1, beta-1-, and beta-2- receptors. Positive findings with these 3 agents, however, should not be considered indicative of a beta-blocker class effect, as shown by the lack of effectiveness of bucindolol and the lesser effectiveness of short-acting metoprolol in clinical trials. Patients who have Stage C HF should be treated with 1 of these 3 beta-blockers.

The relative efficacy among these 3 agents is not known, but available evidence does suggest that beta-blockers can differ in their effects on survival. In one trial, carvedilol (target dose 25 mg twice daily) was compared with immediate-release metoprolol tartrate (target dose 50 mg twice daily). In that trial, carvedilol was associated with a significantly reduced mortality compared with metoprolol tartrate. Although both the dose and the formulation of metoprolol (metoprolol tartrate) used in the above-referenced trial are commonly prescribed by physicians for the treatment of HF, they were neither the dose nor the formulation used in the controlled trial that showed that sustained-release metoprolol (metoprolol succinate) reduces the risk of death. There have been no trials to explore whether the survival benefits of carvedilol are greater than those of sustained-released metoprolol when both are used at the target doses.

Effect of Beta-Blockers in the Management of HF

Beta-blockers have now been evaluated in more than 20 000 patients with HF who participated in more than 20 published placebo-controlled clinical trials. All trials enrolled patients with reduced LVEF (EF less than 35% to 45%) who had already been treated with diuretics and an ACEI, with or without digitalis. These trials recruited many types of patients, including women and the elderly, as well as patients with a wide range of causes and severity of LV dysfunction, but patients with preserved systolic function, low heart rates (less than 65 beats per min), or low systolic blood pressure (less than 85 mm Hg) and those who were hospitalized or who had class IV HF were not recruited or represented a small proportion of the patients who

participated in these published studies. An exception was one trial with carvedilol that enrolled clinically stable patients with NYHA class III and IV symptoms who were free of edema. That trial also demonstrated a reduction in mortality similar to the trials of patients with less advanced disease.

This collective experience indicates that long-term treatment with beta-blockers can lessen the symptoms of HF, improve the clinical status of patients, and enhance the patient's overall sense of well-being. In addition, like ACEIs, beta-blockers can reduce the risk of death and the combined risk of death or hospitalization. These benefits of beta-blockers were seen in patients with or without coronary artery disease and in patients with or without diabetes mellitus, as well as in female and black patients. The favorable effects of beta-blockers were also observed in patients already taking ACEIs, which suggests that combined blockade of the 2 neurohormonal systems can produce additive effects.

Practical Use of Beta-Blockers

Selection of patients

Beta-blockers should be prescribed to all patients with stable HF due to reduced LVEF unless they have a contraindication to their use or have been shown to be unable to tolerate treatment with these drugs.

Because of the favorable effects of beta-blockers on survival and disease progression, treatment with a beta-blocker should be initiated as soon as LV dysfunction is diagnosed. Even when symptoms are mild or have responded to other therapies, beta-blocker therapy is important and should not be delayed until symptoms return or disease progression is documented during treatment with other drugs. Therefore, even if patients do not benefit symptomatically because they have little disability, they should receive treatment with a beta-blocker to reduce the risk of disease progression, future clinical deterioration, and sudden death.

Patients need not be taking high doses of ACEIs before being considered for treatment with a beta-blocker, because most patients enrolled in the beta-blocker trials were not taking high doses of ACEIs. Furthermore, in patients taking a low dose of an ACEI, the addition of a beta-blocker produces a greater improvement in symptoms and reduction in the risk of death than an increase in the dose of the ACEI, even to the target doses used in clinical trials. In patients with current or recent history of fluid retention, beta-blockers should not be prescribed without diuretics, because diuretics are needed to maintain sodium and fluid balance and prevent the exacerbation of fluid retention that can accompany the initiation of beta-blocker therapy.

Which patients are sufficiently stable to be considered for treatment with a beta-blocker? Regardless of the severity of symptoms, patients should not be hospitalized in an intensive care unit, should have no or minimal evidence of



fluid overload or volume depletion, and should not have required recent treatment with an intravenous positive inotropic agent. Those excluded from treatment for these reasons should first receive intensified treatment with other drugs for HF (e.g., diuretics) and then be re-evaluated for beta-blockade after clinical stability has been achieved. Beta-blockers may be considered in patients who have reactive airway disease or asymptomatic bradycardia but should be used with great caution or not at all in patients with persistent symptoms of either condition.

Initiation and maintenance

Treatment with a beta-blocker should be initiated at very low doses (see Table 4), followed by gradual increments in dose if lower doses have been well tolerated. Patients should be monitored closely for changes in vital signs and symptoms during this up-titration period. In addition, because initiation of therapy with a beta-blocker can cause fluid retention, physicians should ask patients to weigh themselves daily and to manage any increase in weight by immediately increasing the dose of concomitantly administered diuretics until weight is restored to pretreatment levels. Planned increments in the dose of a beta-blocker should be delayed until any side effects observed with lower doses have disappeared. Using such a cautious approach, most patients (approximately 85%) enrolled in clinical trials with beta-blockers were able to tolerate short- and long-term treatment with these drugs and achieve the maximum planned trial dose. **Recent data show that beta-blockers can be safely started before discharge even in patients hospitalized for HF, provided they do not require intravenous therapy for HF.**

What dose of a beta-blocker should physicians try to achieve in patients with HF? As with ACEIs, the dose of beta-blockers in controlled clinical trials was not determined by a patient's therapeutic response but was increased until the patient received a prespecified target dose. Low doses were prescribed only if the target doses were not tolerated, and thus, most trials did not evaluate whether low doses would be effective. Therefore, physicians, especially cardiologists and primary care physicians, should make every effort to achieve the target doses of the beta-blockers shown to be effective in major clinical trials.

Once the target dose has been achieved, patients can generally continue long-term therapy with a beta-blocker with little difficulty. Patients should be advised that clinical responses to the drug are generally delayed and may require 2 to 3 months to become apparent. Even if symptoms do not improve, long-term treatment should be maintained to reduce the risk of major clinical events. Abrupt withdrawal of treatment with a beta-blocker can lead to clinical deterioration and should be avoided.

How should clinical deterioration be managed in patients who have been taking a beta-blocker for long periods of time (more than

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3 months)? Because long-term treatment with a beta-blocker reduces the risk of worsening HF, discontinuation of long-term treatment with these drugs after an episode of worsening HF will not diminish and may in fact increase the subsequent risk of clinical decompensation. Consequently, if patients develop fluid retention, with or without mild symptoms, it is reasonable to continue the beta-blocker while the dose of diuretic is increased. However, if the deterioration in clinical status is characterized by hypoperfusion or requires the use of intravenous positive inotropic drugs, it may be prudent to halt or significantly reduce treatment with beta-blockers temporarily until the status of the patient stabilizes. In such patients, positive inotropic agents whose effects are mediated independently of the beta-receptor (e.g., a phosphodiesterase inhibitor such as milrinone) may be preferred. Once stabilized, the beta-blocker should be reintroduced to reduce the subsequent risk of clinical deterioration.

Risks of treatment

Initiation of treatment with a beta-blocker has produced 4 types of adverse reactions that require attention and management, as discussed below.

Fluid retention and worsening HF

Initiation of therapy with a beta-blocker can cause fluid retention, which is usually asymptomatic and is detected primarily by an increase in body weight but which may become sufficiently marked to cause worsening symptoms of HF. Patients with fluid retention before treatment are at greatest risk of fluid retention during treatment, and thus, physicians should ensure that patients are not volume overloaded before a beta-blocker is initiated. Furthermore, physicians should monitor patients closely for increases in weight and for worsening signs and symptoms of HF and should augment the dose of diuretic if weight increases whether or not other signs or symptoms of worsening HF are present. The occurrence of fluid retention or worsening HF is not generally a reason for the permanent withdrawal of treatment. Such patients generally respond favorably to intensification of conventional therapy, and once treated, such patients remain excellent candidates for long-term treatment with a beta-blocker.

Fatigue

Treatment with a beta-blocker can be accompanied by feelings of general fatigue or weakness. In many cases, the sense of lassitude resolves spontaneously within several weeks without treatment, but in some patients, it may be severe enough to limit increments in dose or require the withdrawal of treatment. Complaints of fatigue can generally be managed by a reduction in the dose of the beta-blocker (or the accompanying diuretic), but treatment should be discontinued if the syndrome of weakness is accompanied by evidence

of peripheral hypoperfusion. Reinitiation at a later time or with a different effective beta-blocker may be successful.

Bradycardia and heart block

The slowing of heart rate and cardiac conduction produced by beta-blockers is generally asymptomatic and thus generally requires no treatment; however, if the bradycardia is accompanied by dizziness or lightheadedness or if second- or third-degree heart block occurs, physicians should decrease the dose of the beta-blocker. Physicians should also consider the possibility of drug interactions, because other drugs can cause bradycardia or heart block and may be discontinued. **The role of pacemaker therapy with or without cardiac resynchronization therapy (CRT) to permit the use of beta-blocker therapy is entirely unknown.**

Hypotension

Beta-blockers, especially those that also block alpha-1-receptors, can produce hypotension, which is usually asymptomatic but may produce dizziness, lightheadedness, or blurred vision. For beta-blockers that also block alpha-receptors, such as carvedilol, these vasodilatory side effects are generally seen within 24 to 48 hours of the first dose or the first increments in dose and usually subside with repeated dosing without any change in dose. Physicians may minimize the risk of hypotension by administering the beta-blocker and ACEI at different times during the day. If this is ineffective, the occurrence of hypotension may require a temporary reduction in the dose of the ACEI. Hypotensive symptoms may also resolve after a decrease in the dose of diuretics in patients who are volume depleted, but in the absence of such depletion, relaxation of diuretic therapy may increase the risk or consequences of fluid retention. If hypotension is accompanied by other clinical evidence of hypoperfusion, beta-blocker therapy should be decreased or discontinued pending further patient evaluation.

Digitalis

The digitalis glycosides exert their effects in patients with HF by virtue of their ability to inhibit sodium-potassium ($\text{Na}^+ - \text{K}^+$) adenosine triphosphatase (ATPase). Inhibition of this enzyme in cardiac cells results in an increase in the contractile state of the heart, and for many decades, the benefits of digitalis in HF were ascribed exclusively to this positive inotropic action. However, recent evidence suggests that the benefits of digitalis may be related in part to enzyme inhibition in noncardiac tissues. Inhibition of $\text{Na}^+ - \text{K}^+$ ATPase in vagal afferent fibers acts to sensitize cardiac baroreceptors, which in turn reduces sympathetic outflow from the central nervous system. In addition, by inhibiting $\text{Na}^+ - \text{K}^+$ ATPase in the kidney, digitalis reduces the renal tubular reabsorption of sodium; the resulting increase in

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the delivery of sodium to the distal tubules leads to the suppression of renin secretion from the kidneys. These observations have led to the hypothesis that digitalis acts in HF primarily by attenuating the activation of neurohormonal systems and not as a positive inotropic drug. Although a variety of digitalis glycosides have been used in the treatment of HF for the last 200 years, the most commonly used preparation in the United States is digoxin.

Effect of Digitalis in the Treatment of HF

Several placebo-controlled trials have shown that treatment with digoxin for 1 to 3 months can improve symptoms, quality of life, and exercise tolerance in patients with mild to moderate HF. These benefits have been seen regardless of the underlying rhythm (normal sinus rhythm or atrial fibrillation), cause of HF (ischemic or non-ischemic cardiomyopathy), or concomitant therapy (with or without ACEIs). In a long-term trial that enrolled patients who primarily had class II or III symptoms, treatment with digoxin for 2 to 5 years had no effect on mortality but modestly reduced the combined risk of death and hospitalization.

Practical Use of Digitalis in HF

Selection of patients

Physicians may consider adding digoxin in patients with persistent symptoms of HF during therapy with diuretics, an ACEI (or ARB), and a beta-blocker. Digoxin may also be added to the initial regimen in patients with severe symptoms who have not yet responded symptomatically during treatment with diuretics, an ACEI, and beta-blockers. Alternatively, treatment with digoxin may be delayed until the patient's response to ACEIs and beta-blockers has been defined and be used only in patients who remain symptomatic despite therapy with the neurohormonal antagonists. Yet another strategy is to initiate aldosterone antagonists in this type of symptomatic patient and delay the addition of digoxin except in patients who do not respond or who cannot tolerate aldosterone antagonists. If a patient is taking digoxin but not an ACEI or a beta-blocker, treatment with digoxin should not be withdrawn, but appropriate therapy with the neuro-hormonal antagonists should be instituted. Digoxin is prescribed routinely in patients with HF and chronic atrial fibrillation, but beta-blockers are usually more effective when added to digoxin in controlling the ventricular response, particularly during exercise. Because beta-blockers improve survival and may be effective in controlling rate alone, digoxin should be considered as an adjunctive agent for rate control.

Digoxin is not indicated as primary therapy for the stabilization of patients with an acute exacerbation of HF symptoms, including fluid retention or hypotension. Such patients should first receive appropriate treatment for HF (usually with intravenous medications); therapy with digoxin may be initiated after stabilization as part of an effort to establish a long-term treatment strategy.



Patients should not be given digoxin if they have significant sinus or atrioventricular block, unless the block has been addressed with a permanent pacemaker. The drug should be used cautiously in patients taking other drugs that can depress sinus or atrioventricular nodal function or affect digoxin levels (e.g., amiodarone or a beta-blocker), even though such patients usually tolerate digoxin without difficulty.

Initiation and maintenance

Although a variety of glycosides have been utilized, digoxin is the most commonly used, and it is the only glycoside that has been evaluated in placebo-controlled trials. There is little reason to prescribe other cardiac glycosides for the management of HF.

Therapy with digoxin is commonly initiated and maintained at a dose of 0.125 to 0.25 mg daily. Low doses (0.125 mg daily or every other day) should be used initially if the patient is more than 70 years old, has impaired renal function, or has a low lean body mass. Higher doses (e.g., digoxin 0.375 to 0.50 mg daily) are rarely used or needed in the management of patients with HF. There is no reason to use loading doses of digoxin to initiate therapy in patients with HF.

Doses of digoxin that achieve a concentration of drug in plasma in the range of 0.5 to 1.0 ng per mL are suggested given the limited evidence currently available. There has been no prospective, randomized evaluation of the relative efficacy or safety of different plasma concentrations of digoxin. Retrospective analysis of 2 studies of digoxin withdrawal found that the prevention of worsening HF by digoxin at lower concentrations in plasma (0.5 to 0.9 ng per mL) was as great as that achieved at higher concentrations. In a retrospective analysis of the Digitalis Investigation Group trial, risk-adjusted mortality increased as the plasma concentrations exceeded 1.0 ng per mL. However, the likelihood that reduced clearance of digoxin by renal and hepatic P-glycoprotein transporters reflects HF severity provides an alternate explanation of the relationship of higher plasma levels with mortality, and the most conservative interpretation is that levels of digoxin greater than 1.0 ng per mL were not associated with a superior outcome.

Risks of treatment

When administered with attention to dose and to factors that alter its disposition, digoxin is well tolerated by most patients with HF. The principal adverse reactions occur primarily when digoxin is administered in large doses, but large doses may not be needed to produce clinical benefits. The major side effects include cardiac arrhythmias (e.g., ectopic and re-entrant cardiac rhythms and heart block), gastrointestinal symptoms (e.g., anorexia, nausea, and vomiting), and neurological complaints (e.g., visual disturbances, disorientation, and confusion). Overt digitalis toxicity is commonly associated with serum digoxin levels greater than 2 ng per mL.

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However, toxicity may occur with lower digoxin levels, especially if hypokalemia, hypomagnesemia, or hypothyroidism coexists. The concomitant use of clarithromycin, erythromycin, amiodarone, itraconazole, cyclosporine, verapamil, or quinidine can increase serum digoxin concentrations and may increase the likelihood of digitalis toxicity. The dose of digoxin should be reduced if treatment with these drugs is initiated. Spironolactone does not inhibit the disposition of digoxin; cross-reactivity of some digoxin antibodies with spironolactone confounded earlier attempts to assess the effect of spironolactone on digoxin clearance. In addition, a low lean body mass and impaired renal function can also elevate serum digoxin levels, which may explain the increased risk of digitalis toxicity in elderly patients. Of note, one analysis suggested that women may not benefit from digoxin therapy and may be at increased risk for death with such therapy.

In addition to these established side effects, there is concern that levels of digoxin that previously had been considered to be in the therapeutic range (up to 2 ng per mL) may exert deleterious cardiovascular effects in the long term, even though such levels appear to be well tolerated in the short-term. In one major long-term trial, serum digoxin concentrations in the therapeutic range were associated with an increased frequency of hospitalizations for cardiovascular events other than HF and an increased risk of death due to arrhythmias or MI. These effects neutralized any benefit on survival that might otherwise have been seen as a result of the favorable effect of the drug on HF. These observations have raised the possibility that digoxin doses and serum digoxin concentrations that are generally considered by physicians to be safe may adversely affect the heart. Digoxin should be used with caution or not used at all in post-MI patients, particularly if they have ongoing ischemia.

Ventricular Arrhythmias and Prevention of Sudden Death

Patients with LV dilation and reduced LVEF frequently manifest ventricular tachyarrhythmias, both nonsustained ventricular tachycardia (VT) and sustained VT. The cardiac mortality of patients with all types of ventricular tachyarrhythmias is high. The high mortality results from progressive HF, as well as from sudden death. Sudden death can be decreased meaningfully by the therapies that decrease disease progression, as discussed elsewhere in the full-text guidelines. For instance, clinical trials with beta-blockers have shown a reduction in sudden death, as well as in all-cause mortality, in both postinfarction patients and patients with HF regardless of cause. Aldosterone antagonists decrease sudden death and overall mortality in HF early after MI and in advanced HF. Sudden unexpected death can be decreased further by the use of implanted devices that terminate sustained arrhythmias. Even when specific antiarrhythmic

therapy is necessary to diminish recurrent ventricular tachyarrhythmias and device firings, the frequency and tolerance of arrhythmias may be improved with appropriate therapy for HF. In some cases, definitive therapy of myocardial ischemia or other reversible factors may prevent recurrence of tachyarrhythmia, particularly polymorphic VT, ventricular fibrillation, and nonsustained VT. Nonetheless, implantable defibrillators would be recommended in all patients who have had a life-threatening tachyarrhythmia and have otherwise good prognosis.

Secondary Prevention of Sudden Death

Patients with previous cardiac arrest or documented sustained ventricular arrhythmias have a high risk of recurrent events. Implantation of an ICD has been shown to reduce mortality in cardiac arrest survivors. An ICD is indicated for secondary prevention of death from ventricular tachyarrhythmias in patients with otherwise good clinical function and prognosis, for whom prolongation of survival is a goal. Patients with chronic HF and a low EF who experience syncope of unclear origin have a high rate of subsequent sudden death and should also be considered for placement of an ICD. However, when ventricular tachyarrhythmias occur in a patient with a progressive and irreversible downward spiral of clinical HF decompensation, placement of an ICD is not indicated to prevent recurrence of sudden death, because death is likely imminent regardless of mode. An exception may exist for the small minority of patients for whom definitive therapy such as cardiac transplantation is planned.

Primary Prevention of Sudden Death

Patients with low EF without prior history of cardiac arrest, spontaneous VT, or inducible VT (positive programmed electrical stimulation study) have a risk of sudden death that is lower than for those who have experienced previous events, but it remains significant.

The role of ICDs in the primary prevention of sudden death in patients without prior history of symptomatic arrhythmias has been explored recently in a number of trials. If sustained ventricular tachyarrhythmias can be induced in the electrophysiology laboratory in patients with previous MI or chronic ischemic heart disease, the risk of sudden death in these patients is in the range of 5% to 6% per year and can be improved by ICD implantation.

The role of ICD implantation for the primary prevention of sudden death in patients with HF and low EF and no history of spontaneous or inducible VT has been addressed by several large trials that used only readily available clinical data as entry criteria.

The decision regarding the balance of potential risks and benefits of ICD implantation for an individual patient thus remains a complex

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one. A decrease in incidence of sudden death does not necessarily translate into decreased total mortality, and decreased total mortality does not guarantee a prolongation of survival with meaningful quality of life. This concept is particularly important in patients with limited prognosis owing to advanced HF or other serious comorbidities, because there was no survival benefit observed from ICD implantation until after the first year in 2 of the major trials. Consideration of ICD implantation is thus recommended in patients with EF less than 30% and mild to moderate symptoms of HF and in whom survival with good functional capacity is otherwise anticipated to extend beyond 1 year. Because medical therapy may substantially improve EF, consideration of ICD implants should follow documentation of sustained reduction of EF despite a course of beta-blockers and ACEIs or ARBs; however, ICDs are not warranted in patients with refractory symptoms of HF (Stage D) or in patients with concomitant diseases that would shorten their life expectancy independent of HF. The appropriate management of patients with HF and an EF between 30% and 35% remains controversial.

INTERVENTIONS TO BE CONSIDERED FOR USE IN SELECTED PATIENTS

Controlled clinical trials have shown some interventions to be useful in limited cohorts of patients with HF. Several of these interventions are undergoing active investigation in large-scale trials to determine whether their role in the management of HF might be justifiably expanded, and others have already been validated as useful in specific cohorts.

Isosorbide Dinitrate

Isosorbide dinitrate was one of the first vasodilator agents reported to be useful for chronic therapy of HF. Nitrate therapy may decrease symptoms of dyspnea at night and during exercise and may improve exercise tolerance in patients who have persistent limitations despite optimization of other therapies. Most experience relates to the oral dinitrate and more recently the mononitrate preparations, with little information available about topical nitrate therapy in this population. Recent evidence suggests that nitrates can inhibit abnormal myocardial and vascular growth and may thereby attenuate the process of ventricular remodeling and improve symptoms.

The only common side effects of nitrate therapy are headaches and hypotension. In clinical use, nitrates are frequently prescribed to patients with persistent congestive symptoms. Although the only large trial of nitrates in HF used a combination of nitrates and hydralazine, nitrates predominantly are potent venodilators that

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also have effects on arterial tone when used alone, particularly when systemic vascular resistance is severely elevated. Because they act through cyclic guanosine monophosphate, there is a theoretical reason that they may be titrated up to facilitate weaning of intravenous infusions that act through the same pathway.

There is extensive literature regarding the development of nitrate tolerance. This appears to be minimized by prescription of a “nitrate-free interval” of at least 10 hours and by combination with ACEIs or hydralazine.

Hydralazine

Hydralazine is an arterial vasodilator with relatively little effect on venous tone and cardiac filling pressures. The rationale for its combined use with nitrates was to achieve both venous and arterial vasodilation. In addition to its direct vascular actions, hydralazine in theory may interfere with the biochemical and molecular mechanisms responsible for the progression of HF and the development of nitrate tolerance. There are limited data regarding the use of hydralazine alone in HF.

Hydralazine and Isosorbide Dinitrate

In a large-scale trial that compared the vasodilator combination with placebo, the use of hydralazine and isosorbide dinitrate reduced mortality but not hospitalizations in patients with HF treated with digoxin and diuretics but not an ACEI or beta-blocker. However, in another large-scale trial that compared the vasodilator combination with an ACEI, the ACEI produced more favorable effects on survival, a benefit not evident in the subgroup of patients with class III to IV HF. In both trials, the use of hydralazine and isosorbide dinitrate produced frequent adverse reactions (primarily headache and gastrointestinal complaints), and many patients could not continue treatment at target doses.

Of note, a post hoc retrospective analysis of both vasodilator trials demonstrated particular efficacy of isosorbide dinitrate and hydralazine in the black cohort. A confirmatory trial has been done. **In that trial, which was limited to the black population with HF, the addition of hydralazine and isosorbide dinitrate to standard therapy with an ACEI or a beta-blocker was shown to be of significant benefit.** The benefit was presumed to be related to enhanced nitric oxide bioavailability. Whether this benefit is evident in other patients with HF remains to be investigated. The combination of hydralazine and isosorbide dinitrate should not be used for the treatment of HF in patients who have no prior use of an ACEI and should not be substituted for ACEIs in patients who are tolerating ACEIs without difficulty.

Despite the lack of data with the vasodilator combination in patients who are intolerant of ACEIs, the combined use of

hydralazine and isosorbide dinitrate may be considered as a therapeutic option in such patients. However, compliance with this combination has generally been poor because of the large number of tablets required and the high incidence of adverse reactions. For patients with more severe symptoms and ACEI intolerance, the combination of hydralazine and nitrates is used frequently, particularly when ACEI therapy is limited by hypotension or renal insufficiency. There are, however, no trials addressing the use of isosorbide dinitrate and hydralazine specifically in the population of patients who have persistent symptoms and intolerance to inhibitors of the renin-angiotensin system.

Cardiac Resynchronization Therapy

Approximately one third of patients with low EF and class III to IV symptoms of HF manifest a QRS duration greater than 120 ms. This electrocardiographic representation of abnormal cardiac conduction has been used to identify patients with dyssynchronous ventricular contraction. **While imperfect, no other consensus definition of cardiac dyssynchrony exists as yet, although several echocardiographic measures appear promising.** The mechanical consequences of dyssynchrony include suboptimal ventricular filling, a reduction in LV dP/dt (rate of rise of ventricular contractile force or pressure), prolonged duration (and therefore greater severity) of mitral regurgitation, and paradoxical septal wall motion. Ventricular dyssynchrony has also been associated with increased mortality in HF patients. Dyssynchronous contraction can be addressed by electrically activating the right and left ventricles in a synchronized manner with a biventricular pacemaker device. This approach to HF therapy, commonly called cardiac resynchronization therapy (CRT), may enhance ventricular contraction and reduce the degree of secondary mitral regurgitation. In addition, the short-term use of CRT has been associated with improvements in cardiac function and hemodynamics without an accompanying increase in oxygen utilization, as well as adaptive changes in the biochemistry of the failing heart.

To date, more than 4,000 HF patients with ventricular dyssynchrony have been evaluated in randomized controlled trials of optimal medical therapy alone versus optimal medical therapy plus CRT with or without an ICD. Cardiac resynchronization therapy, when added to optimal medical therapy in persistently symptomatic patients, has resulted in significant improvements in quality of life, functional class, exercise capacity (by peak oxygen uptake) and exercise distance during a 6-minute walk test, and EF in patients randomized to CRT or to the combination of CRT and ICD. There is strong evidence to support the use of CRT to improve symptoms, exercise capacity, quality of life, LVEF, and survival and to decrease hospitalizations in patients with persistently symptomatic HF undergoing optimal

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medical therapy who have cardiac dyssynchrony (as evidenced by a prolonged QRS duration). The use of an ICD in combination with CRT should be based on the indications for ICD therapy.

With few exceptions, resynchronization trials have enrolled patients in normal sinus rhythm. Although the entry criteria specified QRS duration only over 120 ms, the average QRS duration in the large trials was more than 150 ms, with less information demonstrating benefit in patients with lesser prolongation of QRS. **Recommendations regarding CRT for patients with right bundle-branch block, atrial fibrillation, minor conduction abnormality, and pacemaker dependence as well as inadequate medical therapy must await the completion of ongoing or future trials.**

Exercise Training

In the past, patients with HF were advised to avoid physical exertion in the hope that bed rest might minimize symptoms and in the belief that physical activity might accelerate the progression of LV dysfunction; however, it is now understood that a reduction in physical activity (produced by the symptoms of HF or prescribed by physicians treating HF) leads to a state of physical deconditioning that contributes to the symptoms and exercise intolerance of patients with chronic HF. Limitations of activity not only may impair exercise capacity but also may produce adverse psychological effects and impair peripheral vasodilatory responses. These findings have led to the hypothesis that exercise training may improve the clinical status of patients with chronic HF.

Recommendations Concerning Exercise Training

Exercise training should be considered for all stable outpatients with chronic HF who are able to participate in the protocols needed to produce physical conditioning. Exercise training should be used in conjunction with drug therapy.

2. Patients With HF and Normal LVEF

IDENTIFICATION OF PATIENTS

For many years, the syndrome of HF was considered to be synonymous with diminished contractility of the LV, or reduced LVEF. Over the past few years, however, there has been a growing appreciation that a large number of patients with HF have a relatively normal EF, or preserved EF. The pathophysiology of this type of HF has been reviewed in depth, and a large, randomized study that enrolled patients with HF and normal EF has been completed. Currently, a

number of investigators are seeking to clarify the epidemiology, clinical characteristics, and prognosis of patients with HF and a normal LVEF.

Depending on the criteria used to delineate HF and the accepted threshold for defining preserved LVEF, **it is estimated that as many as 20% to 60% of patients with HF have a relatively (or near) normal LVEF** and, in the absence of valvular disease, are believed to have reduced ventricular compliance as a major contributor to the clinical syndrome. Some investigators have found that in a significant number of patients, a tendency to fluid retention and reduced vascular compliance, rather than myocardial stiffness, represent the principal abnormalities. Regardless, abnormal renal sodium handling and arterial stiffness, in addition to myocardial stiffness, are likely to play important pathophysiologic roles in many patients. Diastole is that period in the cardiac cycle during which the myocardium loses its ability to generate force and shorten and returns to an unstressed length and force, and diastolic dysfunction occurs when these events are prolonged, slowed, or are incomplete. It should also be recognized that diastolic function is abnormal in patients with HF and reduced LVEF, as well as those with preserved LVEF. Several recognized myocardial disorders are associated with HF and a normal LVEF, including restrictive cardiomyopathy, obstructive and nonobstructive hypertrophic cardiomyopathy, and infiltrative cardiomyopathies. The vast majority of patients with HF and relatively preserved LVEF have a history of hypertension, and many, if not most, of these patients have evidence of LVH on echocardiography. However, some patients who present with HF and relatively preserved LVEF have no identifiable myocardial pathology. Because these patients usually present with symptoms typical of HF, they should be classified as Stage C. Indeed, most patients will have some detectable structural abnormality of the heart, including LVH, atrial dilation, mitral annular calcification, aortic sclerosis, or myocardial scar.

Heart failure associated with relatively preserved LVEF is most prevalent among elderly women, most of whom have hypertension, diabetes mellitus, or both and often coronary artery disease or atrial fibrillation as well. This observation may be related to the fact that aging has a greater impact on ventricular filling characteristics than on EF. Aging is associated with decreases in the elastic properties of the heart and great vessels, which leads to an increase in systolic blood pressure and an increase in myocardial stiffness. The rate of ventricular filling decreases in part because of structural changes in the heart (due to fibrosis) and because of a decline in relaxation and



compliance. These deleterious effects on diastolic function are exacerbated by a decrease in beta-adrenergic receptor density and a decline in peripheral vasodilator capacity, both of which are characteristic of elderly patients. In addition, elderly patients commonly have associated disorders (e.g., coronary artery disease, diabetes mellitus, aortic stenosis, atrial fibrillation, or obesity), which can adversely affect the diastolic properties of the heart or decrease the time available for ventricular filling. There may also be sex-specific responses to hypertension and diabetes mellitus that make women more susceptible than men to the cumulative effects of aging on diastolic function.

A number of recent investigations have focused on the differences between HF with preserved EF and that with low LVEF. Myocardial infarction or other evidence of atherosclerotic disease appears to be less common in HF with normal LVEF, but hypertension is at least as common in this subgroup. **The morbidity and mortality associated with HF and a relatively preserved LVEF may be nearly as profound as that with low LVEF; frequent and repeated hospitalizations characterize the patient with HF and a normal LVEF.** Most, but not all, series of patients with HF and relatively preserved LVEF have shown better survival than is seen in patients with HF and reduced LVEF; however, these comparisons are difficult to interpret, because it is difficult to be certain that such series do not contain at least some patients in whom the diagnosis of HF is erroneous.

DIAGNOSIS

There have been several proposed criteria by which clinicians and investigators may define HF with a relatively preserved LVEF. In general, a definitive diagnosis can be made when the rate of ventricular relaxation is slowed; this physiological abnormality is characteristically associated with the finding of an elevated LV filling pressure in a patient with normal LV volumes and contractility. In practice, the diagnosis is generally based on the finding of typical symptoms and signs of HF in a patient who is shown to have a normal LVEF and no valvular abnormalities (aortic stenosis or mitral regurgitation, for example) on echocardiography. Every effort should be made to exclude other possible explanations or disorders that may present in a similar manner (see Table 6).

Noninvasive methods (especially those that rely on Doppler echocardiography) have been developed to assist in the diagnosis of HF with normal LVEF, but these tests have significant limitations, because cardiac filling patterns are readily altered by non-specific and transient changes in loading conditions in the heart and by aging, changes in heart rate, or the presence of mitral regurgitation. The analysis of BNP* levels in association with echocardiographic filling patterns can improve diagnostic accuracy. For example, a

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Identification
of Patients/
Diagnosis

Table 6. Differential Diagnosis in a Patient With Heart Failure and Normal Left Ventricular Ejection Fraction

- Incorrect diagnosis of HF
 - Inaccurate measurement of LVEF
 - Primary valvular disease
 - Restrictive (infiltrative) cardiomyopathies
Amyloidosis, sarcoidosis, hemochromatosis
 - Pericardial constriction
 - Episodic or reversible LV systolic dysfunction
 - Severe hypertension, myocardial ischemia
 - HF associated with high metabolic demand (high-output states)
Anemia, thyrotoxicosis, arteriovenous fistulae
 - Chronic pulmonary disease with right HF
 - Pulmonary hypertension associated with pulmonary vascular disorders
 - Atrial myxoma
 - Diastolic dysfunction of uncertain origin
 - Obesity
-

HF = heart failure; LVEF = left ventricular ejection fraction; LV = left ventricular.

normal BNP level along with completely normal diastolic filling parameters makes HF much less likely; however, HF does remain a strictly clinical diagnosis.

PRINCIPLES OF TREATMENT

In contrast to the treatment of HF due to reduced LVEF, few clinical trials are available to guide the management of patients with HF and relatively preserved LVEF. Although controlled studies have been performed with digitalis, ACEIs, ARBs, beta-blockers, and calcium-channel blockers in patients with HF who had a relatively preserved LVEF, for the most part, these trials have been small or have produced inconclusive results. Nevertheless, many patients with HF and normal LVEF are treated with these drugs because of the presence of comorbid conditions (i.e., atrial fibrillation, hypertension, diabetes mellitus, and coronary artery disease). A large, randomized trial recently completed included patients with HF and normal LVEF, which demonstrates that studies in such patients can be accomplished. In that trial, the addition of candesartan to the treatment

*The writing committee intended BNP to indicate B-type natriuretic peptide rather than a specific type of assay. Assessment can be made using assays for BNP or N-terminal proBNP. The two types of assays yield clinically similar information.

regimen for patients with symptomatic HF and relatively preserved LVEF significantly reduced morbidity but did not reach the primary end point.

In the absence of other controlled clinical trials, the management of these patients is based on the control of physiological factors (blood pressure, heart rate, blood volume, and myocardial ischemia) that are known to exert important effects on ventricular relaxation. Likewise, diseases that are known to cause HF with normal LVEF should be treated, such as coronary artery disease, hypertension, or aortic stenosis. Clinically, it seems reasonable to target symptom reduction, principally by reducing cardiac filling pressures at rest and during exertion. Recommendations regarding the use of anti-coagulation and antiarrhythmic agents apply to all patients with HF, irrespective of LVEF.

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Patients With
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(Stage C)

HF and
Normal LVEF

Principles
of Treatment

Potential Treatment Strategies

Hypertension exerts a deleterious effect on ventricular function by causing both structural and functional changes in the heart. Increases in systolic blood pressure have been shown to slow myocardial relaxation, and the resulting hypertrophy may adversely affect passive chamber stiffness. **Physicians should make every effort to control both systolic and diastolic hypertension with effective antihypertensive therapy in accordance with published guidelines.** Consideration should at least be given to achieving target levels of blood pressure lower than those recommended for patients with uncomplicated hypertension (e.g., less than 130 mm Hg systolic and less than 80 mm Hg diastolic). Because myocardial ischemia can impair ventricular relaxation, coronary revascularization should be considered in patients with coronary artery disease in whom symptomatic or demonstrable myocardial ischemia is believed to be exerting a deleterious effect on cardiac function (for more information, see the ACC/AHA 2004 Guideline Update for Coronary Artery Bypass Graft Surgery).



Because tachycardia can shorten the time available for ventricular filling and coronary perfusion, drugs that slow the heart rate or the ventricular response to atrial arrhythmias (e.g., beta-blockers, digoxin, and some calcium-channel blockers) can provide symptomatic relief in patients with HF and normal LVEF. Similarly, patients with HF and preserved LVEF may be particularly sensitive to loss of atrial kick, which supports a potential benefit for restoration of sinus rhythm in patients with atrial fibrillation. The benefits of restoring sinus rhythm in these individuals are less clear, and the large trials of rhythm versus rate control in atrial fibrillation published recently have excluded patients with HF. Moreover, the presence of systolic or diastolic dysfunction may diminish the efficacy and enhance the toxicity of drugs used to achieve and maintain sinus rhythm.

Circulating blood volume is a major determinant of ventricular filling pressure, and the use of diuretics may improve breathlessness in patients with HF and normal LVEF as well as those with reduced LVEF. Other possible agents used to reduce diastolic filling pressures are nitrates or agents that block neurohumoral activation. Hypotension may be a significant problem in this population, especially in the very elderly, because they can be quite sensitive to preload reduction.

3. Prevention of Thromboembolic Events

Patients with chronic HF are at increased risk of thromboembolic events due to stasis of blood in dilated hypokinetic cardiac chambers and in peripheral blood vessels and perhaps due to increased activity of procoagulant factors. However, in large-scale studies, the risk of thromboembolism in clinically stable patients has been low (1% to 3% per year), even in those with very depressed EFs and echocardiographic evidence of intracardiac thrombi. These rates are sufficiently low to limit the detectable benefit of anticoagulation in these patients.

In several retrospective analyses, the risk of thromboembolic events was not lower in patients with HF taking warfarin than in patients not treated with antithrombotic drugs. The use of warfarin was associated with a reduction in major cardiovascular events and death in patients with HF in one retrospective analysis but not in another. A randomized trial comparing the outcome of patients with HF and low EF assigned to aspirin, warfarin, or clopidogrel was completed recently. Unfortunately, low enrollment in the trial precluded definitive conclusions about efficacy, but no therapy appeared to be superior. Another trial is currently under way comparing aspirin with warfarin in patients with reduced LVEF and may provide more definitive data upon which to base recommendations.

RECOMMENDATIONS CONCERNING MANAGEMENT

In the absence of definitive trials, it is not clear how anticoagulants should be prescribed in patients with HF. Despite the lack of supportive data, some physicians prescribe anticoagulants to all patients with markedly depressed EFs and dilated hearts. Others would advocate the use of warfarin in patients who are known to harbor a cardiac thrombus, even though many thrombi detected by echocardiography do not embolize, and many embolic events are probably related to thrombi that are not visualized. Anticoagulation with warfarin is most justified in patients with HF who have experienced a previous embolic event or who have paroxysmal or persistent atrial fibrillation. Anticoagulation should also be considered in patients with underlying disorders that may be associated with an increased thromboembolic risk (e.g., amyloidosis or LV noncompaction) and in patients with familial dilated cardiomyopathy and a history of thromboembolism in first-degree relatives.

Therapy

Patients With
Refractory
End-Stage HF
(Stage D)

Management
of Fluid Status
Utilization of
Neurohormonal
Inhibitors

B. Patients With Refractory End-Stage HF (Stage D)

Most patients with HF due to reduced LVEF respond favorably to pharmacological and nonpharmacological treatments and enjoy a good quality of life and enhanced survival; however, some patients do not improve or experience rapid recurrence of symptoms despite optimal medical therapy. Such patients characteristically have symptoms at rest or on minimal exertion, including profound fatigue; cannot perform most activities of daily living; frequently have evidence of cardiac cachexia; and typically require repeated and/or prolonged hospitalizations for intensive management. These individuals represent the most advanced stage of HF and should be considered for specialized treatment strategies, such as mechanical circulatory support, continuous intravenous positive inotropic therapy, referral for cardiac transplantation, or hospice care.

Before a patient is considered to have refractory HF, physicians should confirm the accuracy of the diagnosis, identify any contributing conditions, and ensure that all conventional medical strategies have been optimally employed. Measures listed as class I recommendations for patients in Stages A, B, and C are also appropriate for patients in end-stage HF. When no further therapies are appropriate, careful discussion of the prognosis and options for end-of-life care should be initiated.

1. Management of Fluid Status

Many patients with advanced HF have symptoms that are related to the retention of salt and water and thus will respond favorably to interventions designed to restore sodium balance. Hence, a critical step in the successful management of end-stage HF is the recognition and meticulous control of fluid retention.

In most patients with chronic HF, volume overload can be treated adequately with low doses of a loop diuretic combined with moderate dietary sodium restriction; however, as HF advances, the accompanying decline in renal perfusion can limit the ability of the kidneys to respond to diuretic therapy. In such patients, the control of fluid retention may require progressive increments in the dose of a loop diuretic and frequently the addition of a second diuretic that has a complementary mode of action (e.g., metolazone). If the

patient continues to exhibit evidence of volume overload

despite these measures, hospitalization is generally required for further adjustment of therapy, possibly including intravenous dopamine or dobutamine.

This strategy can elicit a marked increase in urine volume, but such a diuresis is frequently accompanied by worsening azotemia, especially if patients are also being treated with an ACEI.

Provided that renal function stabilizes, small or moderate elevations of blood urea nitrogen and

serum creatinine should not lead to efforts to minimize

the intensity of therapy; however, if the degree of renal dysfunction is severe or if the edema becomes resistant to treatment, ultrafiltration or hemofiltration may be needed to achieve adequate control of fluid retention. The use of such mechanical methods of fluid removal can produce meaningful clinical benefits in patients with diuretic-resistant HF and may restore responsiveness to conventional doses of loop diuretics.

In general, patients should not be discharged from the hospital until a stable and effective diuretic regimen is established, and ideally, not until euvolemia is achieved. Patients who are sent home before these goals are reached are at high risk of recurrence of fluid retention and early readmission, because unresolved edema may itself attenuate the response to diuretics. Once euvolemia is achieved, the patient's dry weight can be defined and used as a continuing target for the adjustment of diuretic doses. Many patients are able to modify their own diuretic regimen in response to changes in weight that exceed a predefined range. The restriction of dietary sodium (to 2 g daily or less) can greatly assist in the maintenance of volume balance. Patients with persistent or recurrent fluid retention despite sodium restriction and high-dose diuretic use may benefit from review of fluid intake and restriction to 2 liters daily.

The ongoing control of fluid retention may be enhanced by enrollment in an HF program, which can provide the close surveillance and education needed for the early recognition and treatment of volume overload.



2. Utilization of Neurohormonal Inhibitors

Controlled trials suggest that patients with advanced HF respond favorably to treatment with both ACEIs and beta-blockers in a manner similar to those with mild to moderate disease. However, because neurohormonal mechanisms play an important role in the support of circulatory homeostasis as HF progresses, neurohormonal antagonism may be less well tolerated by patients with severe symptoms than by patients with mild symptoms. Patients who are at the end stage of their disease are at particular risk of developing hypotension and renal insufficiency after the administration of an ACEI and of experiencing worsening HF after treatment with a beta-blocker. As a result, patients with refractory HF may tolerate only small doses of these neurohormonal antagonists or may not tolerate them at all.

Therapy

Patients With Refractory End-Stage HF (Stage D)

Vasodilators and Positive Inotropic Agents
Prevention of Thromboembolic Events

Recommendations Concerning Management

Consequently, physicians should exercise great care when considering the use of both ACEIs and beta-blockers in patients with refractory HF. Treatment with either type of drug should not be initiated in patients who have systolic blood pressures less than 80 mm Hg or who have signs of peripheral hypoperfusion. In addition, patients should not be started on a beta-blocker if they have significant fluid retention or if they recently required treatment with an intravenous positive inotropic agent. Treatment with an ACEI or beta-blocker should be initiated in very low doses, and patients should be monitored closely for signs or symptoms of intolerance. If low doses are tolerated, further dosage increments may be considered but may not be tolerated. However, clinical trials with lisinopril and carvedilol suggest that even low doses of these drugs may provide important benefits.

Alternative pharmacological treatments may be considered for patients who cannot tolerate ACEIs or beta-blockers. A combination of nitrates and hydralazine has been reported to have favorable effects on survival in patients with mild to moderate symptoms who were not taking an ACEI or a beta-blocker, but the utility of this vasodilator combination in patients with end-stage disease who are being given these neurohormonal antagonists remains unknown. In addition, many patients experience headaches or gastrointestinal distress with these direct-acting vasodilators, which can prevent patients from undergoing long-term treatment. Spironolactone has been reported to prolong life and reduce the risk of hospitalization for HF in patients with advanced disease; however, the evidence supporting the use of the drug has been derived in patients who have preserved renal function, and the drug can produce dangerous hyperkalemia in patients with impaired renal function. Finally, although ARBs are frequently considered as alternatives to ACEIs because of the low incidence of cough and angioedema with these medications, it is not clear that ARBs are as effective as ACEIs, and they are as likely as ACEIs to produce hypotension or renal insufficiency.

3. Intravenous Peripheral Vasodilators and Positive Inotropic Agents

Patients with refractory HF are hospitalized frequently for clinical deterioration, and during such admissions, they commonly receive infusions of both positive inotropic agents (dobutamine, dopamine, or milrinone) and vasodilator drugs (nitroglycerin, nitroprusside, or nesiritide) in an effort to improve cardiac performance, facilitate diuresis, and promote clinical stability. Some physicians have advocated the placement of pulmonary artery catheters in patients with refractory HF, with the goal of obtaining hemodynamic measurements that might be used to guide the selection and titration of therapeutic agents. However, the logic of this approach has been questioned, because many useful drugs for HF produce benefits by mechanisms that cannot be evaluated by measuring their short-term hemodynamic effects. Regardless of whether invasive hemodynamic monitoring is used, once the clinical status of the patient has stabilized, every effort should be made to devise an oral regimen that can maintain symptomatic improvement and reduce the subsequent risk of deterioration. Assessment of the adequacy and tolerability of orally based strategies may necessitate observation in the hospital for at least 48 hours after the infusions are discontinued.

Patients who cannot be weaned from intravenous to oral therapy despite repeated attempts may require placement of an indwelling intravenous catheter to allow for the continuous infusion of dobutamine or milrinone, or as has been used more recently, nesiritide. Such a strategy is commonly used in patients who are awaiting cardiac transplantation, but it may also be used in the outpatient setting in patients who otherwise cannot be discharged from the hospital.

The decision to continue intravenous infusions at home should not be made until all alternative attempts to achieve stability have failed repeatedly, because such an approach can present a major burden to the family and health services and may ultimately increase the risk of death. However, continuous intravenous support can provide palliation of symptoms as part of an overall plan to allow the patient to die with comfort at home. The use of continuous intravenous support to allow hospital discharge should be distinguished from the intermittent administration of infusions of such agents to patients who have been successfully weaned from inotropic support.





III. End-of-Life Considerations

Although issues surrounding end-of-life care deserve attention for all chronic terminal diseases, several general principles merit particular discussion in the context of chronic HF. Education of both patient and family regarding the expected or anticipated course of illness, final treatment options, and planning should be undertaken before the patient becomes too ill to participate in decisions. Discussions regarding treatment preferences, living wills, and advance directives should encompass a variety of likely contingencies that include responses to a potentially reversible exacerbation of HF, a cardiac arrest, a sudden catastrophic event such as a severe cerebrovascular accident, and worsening of major coexisting noncardiac conditions. In reviewing these issues with families, short-term intervention in anticipation of rapid recovery should be distinguished from prolonged life support without reasonable expectation of a return to good functional capacity.

When the limitations imposed by HF alone or in combination with other severe conditions become intolerable, however, resuscitation may no longer be desired by the patient. **At the end of life, it is important to understand which aspects of further care the patient wishes to forego.** In some cases, the patient may want full supportive care while conscious, other than actual resuscitation; in other circumstances, hospitalization may no longer be desired for any intervention. Any decision to forego resuscitation should lead to possible deactivation of the life-saving function of an implanted defibrillation device; the poor functional status of any patient should also influence the decision regarding implantation of such a device in the first place. To observe both the intent and the directives of the patient and family, it is highly desirable that outpatient, inpatient, and crisis management be supervised by the same team to diminish the hazards of fragmented care during this period. The patient should be encouraged to choose in advance a person to assume legal authority (i.e., designated power of attorney or healthcare proxy) for healthcare matters when the patient cannot be involved in decisions. That individual should serve as the contact point for the team. Rapid communications with this team will reduce the conflicts and uncertainties that may arise when patients are first seen in an emergency setting by physicians not normally involved in their care. The standing-care plans for each patient need to be

quickly accessible to all personnel likely to be involved in the patient's care. Professionals caring for patients with advanced HF should have realistic expectations for survival and communicate those accurately to patients and families. Also, the professionals should provide realistic recommendations for procedures being done within the final days of life that do not add to the hope of recovery or improvement in life quality. Finally, greater attention and research need to be devoted to the provision of comfort measures in the final days of life, including relief of pain and dyspnea.

Hospice services have only recently been extended to patients dying of HF. Originally developed for patients with end-stage cancer, the focus of hospice care has now been expanded to include the relief of symptoms other than pain. This is appropriate because the suffering of patients with HF is characteristically linked to symptoms of breathlessness, and thus, compassionate care may require the frequent administration of intravenous diuretics and, in some cases, the continuous infusion of positive inotropic agents rather than only the use of potent analgesics. However, many patients dying of HF do describe pain during the final days. Physicians caring for these patients should become familiar with the prescription of anxiolytics, sleeping medications, and narcotics to ease distress during the last days.

Ultimately, the decisions regarding when end of life is nearing reflect a complex interaction between objective information and subjective information, emotions, and patient and family readiness. Ideally, these decisions would be made in conjunction with the individual or team most experienced in caring for advanced HF or in collaboration and/or consultation with such an expert. As we become more familiar with the steps in progression to end-stage HF in this era, the current abrupt transition from aggressive intervention to comfort and bereavement care will be softened by a gradual and progressive emphasis on palliation until it dominates the final days of care.



Abbreviations

ACC	American College of Cardiology
ACE	angiotensin converting enzyme
ACEI	angiotensin converting enzyme inhibitor
AHA	American Heart Association
ARB	angiotensin II receptor blocker
ATPase	adenosine triphosphatase
BNP*	B-type natriuretic peptide
CRT	cardiac resynchronization therapy
EF	ejection fraction
HF	heart failure
ICD	implantable cardioverter-defibrillator
LV	left ventricular; left ventricle
LVEF	left ventricular ejection fraction
LVH	left ventricular hypertrophy
MI	myocardial infarction
NYHA	New York Heart Association
VT	ventricular tachycardia

*The writing committee intended BNP to indicate B-type natriuretic peptide rather than a specific type of assay. Assessment can be made using assays for BNP or N-terminal proBNP. The two types of assays yield clinically similar information.

