
ACC/AHA PRACTICE GUIDELINES—FULL TEXT

ACC/AHA Guidelines for the Evaluation and Management of Chronic Heart Failure in the Adult

A Report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (Committee to Revise the 1995 Guidelines for the Evaluation and Management of Heart Failure)

Developed in Collaboration with the International Society for Heart and Lung Transplantation

Endorsed by the Heart Failure Society of America

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PREAMBLE

It is important that the medical profession play a significant role in critically evaluating the use of diagnostic procedures and therapies in the management or prevention of disease

states. Rigorous and expert analysis of the available data documenting relative benefits and risks of those procedures and therapies can produce helpful guidelines that improve the effectiveness of care, optimize patient outcomes, and affect the overall cost of care favorably by focusing resources on the most effective strategies.

The American College of Cardiology (ACC) and the American Heart Association (AHA) have jointly engaged in the production of such guidelines in the area of cardiovascular disease since 1980. This effort is directed by the ACC/AHA Task Force on Practice Guidelines, whose charge is to develop and revise practice guidelines for important cardiovascular diseases and procedures. Experts in the subject under consideration are selected from both organizations to examine subject-specific data and write guidelines. The process includes additional representatives from other medical practitioner and specialty groups where appropriate. Writing groups are specifically charged to perform a formal literature review, weigh the strength of evidence for or against a particular treatment or procedure, and include estimates of expected health outcomes where data exist. Patient-specific modifiers, comorbidities and issues of patient preference that might influence the choice of particular tests or therapies are considered as well as frequency of follow-up and cost-effectiveness.

The ACC/AHA Task Force on Practice Guidelines makes every effort to avoid any actual or potential conflicts of interest that might arise as a result of an outside relationship or personal interest of a member of the writing panel. Specifically, all members of the writing panel are asked to provide disclosure statements of all such relationships that might be perceived as real or potential conflicts of interest. These statements are reviewed by the parent task force, reported orally to all members of the writing panel at the first meeting, and updated as changes occur.

These practice guidelines are intended to assist physicians in clinical decision making by describing a range of generally acceptable approaches for the diagnosis, management, or prevention of specific diseases or conditions. These guidelines attempt to define practices that meet the needs of most patients in most circumstances. The ultimate judgment regarding care of a particular patient must be made by the physician and patient in light of all of the circumstances presented by that patient.

These guidelines were approved for publication by the governing bodies of the ACC and the AHA and have been officially endorsed by the Heart Failure Society of America and the International Society of Heart and Lung Transplantation. The guidelines will be reviewed annually after publication and considered current unless the ACC/AHA Task Force on Practice Guidelines revises or withdraws them from circulation. The executive summary and recommendations are published in the December 2001 issue of the *Journal of the American College of Cardiology*. The full-text guideline is posted on the World Wide Web sites of the American College of Cardiology (www.acc.org)

and the American Heart Association (www.americanheart.org). Copies of the full text and the executive summary are available from both organizations.

Raymond J. Gibbons, MD, FACC
Chair, ACC/AHA Task Force on Practice Guidelines

I. INTRODUCTION

Heart failure (HF) is a major public health problem in the United States. Nearly 5 million patients in this country have HF, and nearly 500,000 patients are diagnosed with HF for the first time each year. The disorder is the underlying reason for 12 to 15 million office visits and 6.5 million hospital days each year (1). During the last 10 years the annual number of hospitalizations has increased from approximately 550,000 to nearly 900,000 for HF as a primary diagnosis and from 1.7 to 2.6 million for HF as a primary or secondary diagnosis (2). Nearly 300,000 patients die of HF as a primary or contributory cause each year, and the number of deaths has increased steadily despite advances in treatment.

Heart failure is primarily a disease of the elderly (3). Approximately 6% to 10% of people older than 65 years have HF (4), and approximately 80% of patients hospitalized with HF are more than 65 years old (2). Heart failure is the most common Medicare diagnosis-related group (DRG), and more Medicare dollars are spent for the diagnosis and treatment of HF than for any other diagnosis (5). The total inpatient and outpatient costs for HF in 1991 were approximately \$38.1 billion, which was approximately 5.4% of the health care budget that year (1). In the United States approximately \$500 million annually is spent on drugs for the treatment of HF.

The ACC and the AHA first published guidelines for the evaluation and management of HF in 1995. Since that time, a great deal of progress has been made in development of both pharmacological and nonpharmacological approaches to treatment for this common, costly, disabling, and generally fatal disorder. For this reason, the 2 organizations believed that the time was right to reassess and update these guidelines, fully recognizing that the optimal therapy of HF remains a work in progress and that future guidelines will supercede these.

The writing committee was composed of 7 members who represented the ACC and AHA, as well as invited participants from the American College of Chest Physicians, the Heart Failure Society of America, the International Society for Heart and Lung Transplantation, the American Academy of Family Physicians, and the American College of Physicians–American Society of Internal Medicine. Both the academic and private practice sectors were represented. This document was reviewed by 3 official reviewers nominated by the ACC, 3 official reviewers nominated by the AHA, 1 reviewer nominated by the Heart Failure Society of America, 1 reviewer nominated by the International Society for Heart and Lung Transplantation, 1 reviewer nominated

from the American Academy of Family Physicians, 1 reviewer nominated by the National Heart Foundation of Australia, the ACC Hypertensive Disease Committee, and 16 content reviewers.

In formulating the present document, the writing committee decided to take a new approach to the classification of HF, that emphasized both the evolution and progression of the disease. In doing so, we identified 4 stages of HF. **Stage A** identifies the patient who is at high risk for developing HF but has no structural disorder of the heart; **Stage B** refers to a patient with a structural disorder of the heart but who has never developed symptoms of HF; **Stage C** denotes the patient with past or current symptoms of HF associated with underlying structural heart disease; and **Stage D** designates the patient with end-stage disease who requires specialized treatment strategies such as mechanical circulatory support, continuous inotropic infusions, cardiac transplantation, or hospice care. Only the latter 2 stages, of course, qualify for the traditional clinical diagnosis of HF for diagnostic or coding purposes. This classification recognizes that there are established risk factors and structural prerequisites for the development of HF and that therapeutic interventions performed even before the appearance of left ventricular dysfunction or symptoms can reduce the morbidity and mortality of HF. This classification system is intended to complement but not to replace the New York Heart Association (NYHA) functional classification, which primarily gauges the severity of symptoms in patients who are in Stage C or D. It has been recognized for many years, however, that the NYHA functional classification reflects a subjective assessment by a physician and changes frequently over short periods of time and that the treatments used do not differ significantly across the classes. Therefore, the committee believed that a staging system was needed that would reliably and objectively identify patients in the course of their disease and would be linked to treatments that were uniquely appropriate at each stage of illness. According to this new approach, patients would only be expected to advance from one stage to the next, unless progression of the disease was slowed or stopped by treatment. This new classification scheme adds a useful dimension to our thinking about HF that is similar to that achieved by staging systems for other disorders (e.g., those used in the classification of cancer).

All recommendations provided in this document follow the format of previous ACC/AHA guidelines:

Class I: Conditions for which there is evidence and/or general agreement that a given procedure/therapy is useful and effective.

Class II: Conditions for which there is conflicting evidence and/or a divergence of opinion about the usefulness/efficacy of performing the procedure/therapy.

Class IIa: Weight of evidence/opinion is in favor of usefulness/efficacy.

Class IIb: Usefulness/efficacy is less well established by evidence/opinion.

Class III: Conditions for which there is evidence and/or general agreement that a procedure/therapy is not useful/effective and in some cases may be harmful.

The recommendations listed in this document are evidence-based, whenever possible. Pertinent medical literature in the English language was identified through a series of computerized literature searches (including Medline and EMBASE) and a manual search of selected articles. References selected and published in this document are representative but not all-inclusive.

The levels of evidence upon which these recommendations are based were ranked as **Level A** if the data were derived from multiple randomized clinical trials, **Level B** when data were derived from a single randomized trial or nonrandomized studies, and **Level C** when the consensus opinion of experts was the primary source of recommendation. The strength of evidence does not necessarily reflect the strength of a recommendation. A treatment may be considered controversial although it has been evaluated in controlled clinical trials; conversely, a strong recommendation may be based on years of clinical experience and be supported only by historical data or by no data at all.

The committee elected to focus this document on the prevention of HF as well as on the evaluation and management of chronic HF in the adult patient with left ventricular systolic and diastolic dysfunction. It specifically did not consider acute HF, which might merit a separate set of guidelines and is addressed in part in the ACC/AHA Guidelines for the Management of Patients With Acute Myocardial Infarction (6). We have also excluded HF in children, both because the underlying causes of HF in children differ from those in adults and because none of the controlled trials of treatments for HF have included children. We have not considered the management of HF due to primary valvular disease [see ACC/AHA Guidelines on Management of Patients With Valvular Heart Disease (7)] or congenital malformations, and we have not included recommendations for the treatment of specific myocardial disorders (e.g., hemochromatosis, sarcoidosis, or amyloidosis).

These practice guidelines are intended to assist physicians in clinical decision-making by describing a range of generally acceptable approaches for the prevention, diagnosis, and management of HF. The guidelines attempt to define practices that meet the needs of most patients under most circumstances. However, the ultimate judgment regarding the care of a particular patient must be made by the physician in light of all of the circumstances that are relevant to that patient. The various therapeutic strategies described in this document can be viewed as a checklist to be considered for each patient in an attempt to individualize treatment for an evolving disease process. Every patient is unique, not only in terms of his or her cause and course of HF, but also in terms

of his or her personal and cultural approach to the disease. Guidelines can only provide an outline for evidence-based decisions or recommendations for individual care; these guidelines are meant to provide that outline.

II. CHARACTERIZATION OF HF AS A CLINICAL SYNDROME

A. Definition of HF

Heart failure is a complex clinical syndrome that can result from any structural or functional cardiac disorder that impairs the ability of the ventricle to fill with or eject blood. The cardinal manifestations of HF are dyspnea and fatigue, which may limit exercise tolerance, and fluid retention, which may lead to pulmonary congestion and peripheral edema. Both abnormalities can impair the functional capacity and quality of life of affected individuals, but they do not necessarily dominate the clinical picture at the same time. Some patients have exercise intolerance but little evidence of fluid retention, whereas others complain primarily of edema and report few symptoms of dyspnea or fatigue. Because not all patients have volume overload at the time of initial or subsequent evaluation, the term “heart failure” is preferred over the older term “congestive heart failure.”

The clinical syndrome of HF may result from disorders of the pericardium, myocardium, endocardium, or great vessels, but the majority of patients with HF have symptoms due to an impairment of left ventricular function. Heart failure may be associated with a wide spectrum of left ventricular functional abnormalities, which may range from the predominantly diastolic dysfunction of a normal-sized chamber with normal emptying but impaired filling to the predominantly systolic dysfunction of a markedly dilated chamber with reduced wall motion but preserved filling. In many patients, abnormalities of systolic and diastolic dysfunction coexist. The principal hallmark of patients with predominant systolic dysfunction is a depressed left ventricular ejection fraction (generally less than 40%); in contrast, patients with predominant diastolic dysfunction typically have an impairment of 1 or more indices of ventricular filling. Patients with predominant diastolic dysfunction have a different natural history and require different treatment strategies than patients with predominant systolic dysfunction (see Section VI. Diastolic Dysfunction).

Coronary artery disease is the cause of HF in about two thirds of patients with left ventricular systolic dysfunction (8). The remainder have a nonischemic cardiomyopathy, which may have an identifiable cause (e.g., hypertension, thyroid disease, valvular disease, alcohol use, or myocarditis) or may have no known cause (e.g., idiopathic dilated cardiomyopathy).

It should be emphasized that HF is not equivalent to cardiomyopathy or to left ventricular dysfunction; these latter terms describe possible structural reasons for the development of HF. Instead, HF is a clinical syndrome that is characterized by specific symptoms (dyspnea and fatigue) and signs (fluid retention). There is no diagnostic test for HF,

because it is largely a clinical diagnosis that is based on a careful history and physical examination.

B. HF as a Symptomatic Disorder

The approach that is most commonly used to quantify the degree of functional limitation imposed by HF is one first developed by the NYHA. This system assigns patients to 1 of 4 functional classes, depending on the degree of effort needed to elicit symptoms: patients may have symptoms of HF at rest (class IV), on less-than-ordinary exertion (class III), on ordinary exertion (class II), or only at levels of exertion that would limit normal individuals (class I). Although the functional class tends to deteriorate over periods of time, most patients with HF do not typically show an uninterrupted and inexorable worsening of symptoms. Instead, the severity of symptoms characteristically fluctuates even in the absence of changes in medications, and changes in medications and diet can have marked favorable or adverse effects on functional capacity in the absence of measurable changes in ventricular function.

The mechanisms responsible for the exercise intolerance of patients with chronic HF have not been clearly defined. Although HF is generally regarded as a hemodynamic disorder, many studies have indicated that there is a poor relation between cardiac performance and the symptoms produced by the disease. Patients with a very low ejection fraction are frequently asymptomatic, whereas patients with preserved left ventricular systolic function may have severe disability. The apparent discordance between the severity of systolic dysfunction and the degree of functional impairment is not well understood but may be explained in part by alterations in ventricular distensibility, valvular regurgitation, pericardial restraint, and right ventricular function. In addition, in ambulatory patients, many noncardiac factors may contribute importantly to exercise intolerance. These factors include but are not limited to changes in peripheral vascular function, skeletal muscle physiology, pulmonary dynamics, and neurohormonal and reflex autonomic activity. The existence of these noncardiac factors may explain why the hemodynamic improvement produced by therapeutic agents in patients with chronic HF may not be immediately or necessarily translated into clinical improvement. Although pharmacological interventions may produce rapid changes in hemodynamic variables, signs and symptoms may improve slowly over weeks or months or not at all.

C. HF as a Progressive Disorder

Left ventricular dysfunction begins with some injury to or stress on the myocardium and is generally a progressive process, even in the absence of a new identifiable insult to the heart. The principal manifestation of such progression is a change in the geometry of the left ventricle such that the chamber dilates, hypertrophies, and becomes more spherical—a process referred to as cardiac remodeling. This change in chamber size not only increases the hemodynamic stresses on the walls of the failing heart and depresses its

mechanical performance but also increases the magnitude of regurgitant flow through the mitral valve. These effects, in turn, serve to sustain and exacerbate the remodeling process. Cardiac remodeling generally precedes the development of symptoms (occasionally by months or even years), continues after the appearance of symptoms, and contributes importantly to worsening of symptoms despite treatment.

What factors can accelerate the process of left ventricular remodeling? Although many mechanisms may be involved, there is substantial evidence that the activation of endogenous neurohormonal systems may play an important role in cardiac remodeling and thereby in the progression of HF. Patients with HF have elevated circulating or tissue levels of norepinephrine, angiotensin II, aldosterone, endothelin, vasopressin, and cytokines, which can act (alone or in concert) to adversely affect the structure and function of the heart. These neurohormonal factors not only increase the hemodynamic stresses on the ventricle by causing sodium retention and peripheral vasoconstriction, but may also exert direct toxic effects on cardiac cells and stimulate myocardial fibrosis, which can further alter the architecture and impair the performance of the failing heart.

The evolution and progression of HF can be appropriately characterized by considering 4 stages of the disease as described in the Introduction and in Table 1. This staging system recognizes that HF, like coronary artery disease, has established risk factors and structural prerequisites; that the evolution of HF has asymptomatic and symptomatic phases; and that specific treatments targeted at each stage can reduce the morbidity and mortality of HF (Fig. 1).

III. CLINICAL ASSESSMENT

A. Initial Evaluation of Patients

1. Identification of Patients

In general, patients with left ventricular dysfunction or HF present to the physician in 1 of 3 ways:

(1) *With a syndrome of decreased exercise tolerance.* Most patients with HF seek medical attention with complaints of a reduction in their effort tolerance due to dyspnea and/or fatigue. These symptoms, which may occur at rest or during exercise, may be attributed inappropriately by the patient and/or physician to aging, to other physiological abnormalities (e.g., deconditioning), or to other disorders (e.g., pulmonary disease). Therefore, in a patient whose exercise capacity is limited by dyspnea or fatigue, the physician must determine whether the principal cause is HF or another abnormality. Elucidation of the precise reason for exercise intolerance can be difficult because these disorders may coexist in the same patient. A clear distinction can sometimes be made only by measurements of gas exchange or blood oxygen saturation or by invasive hemodynamic measurements during graded levels of exercise [see ACC/AHA Guidelines for Exercise Testing (9)].

(2) *With a syndrome of fluid retention.* Patients may present with complaints of leg or abdominal swelling as their

Table 1. Stages of HF

Stage	Description	Examples
A	Patients at high risk of developing HF because of the presence of conditions that are strongly associated with the development of HF. Such patients have no identified structural or functional abnormalities of the pericardium, myocardium, or cardiac valves and have never shown signs or symptoms of HF.	Systemic hypertension; coronary artery disease; diabetes mellitus; history of cardiotoxic drug therapy or alcohol abuse; personal history of rheumatic fever; family history of cardiomyopathy.
B	Patients who have developed structural heart disease that is strongly associated with the development of HF but who have never shown signs or symptoms of HF.	Left ventricular hypertrophy or fibrosis; left ventricular dilatation or hypocontractility; asymptomatic valvular heart disease; previous myocardial infarction.
C	Patients who have current or prior symptoms of HF associated with underlying structural heart disease.	Dyspnea or fatigue due to left ventricular systolic dysfunction; asymptomatic patients who are undergoing treatment for prior symptoms of HF.
D	Patients with advanced structural heart disease and marked symptoms of HF at rest despite maximal medical therapy and who require specialized interventions.	Patients who are frequently hospitalized for HF and cannot be safely discharged from the hospital; patients in the hospital awaiting heart transplantation; patients at home receiving continuous intravenous support for symptom relief or being supported with a mechanical circulatory assist device; patients in a hospice setting for the management of HF.

HF indicates heart failure.

primary (or only) symptom. In these patients, the impairment of exercise tolerance may occur so gradually that it may not be noted unless the patient is questioned carefully and specifically about a change in activities of daily living.

(3) *With no symptoms or symptoms of another cardiac or noncardiac disorder.* During their evaluation for a disorder other than HF (e.g., an acute myocardial infarction, an arrhythmia, or a pulmonary or systemic thromboembolic event), these patients are found to have evidence of cardiac enlargement or dysfunction.

2. Identification of a Structural Abnormality

A complete history and physical examination are the first steps in evaluating the structural abnormality or cause responsible for the development of HF. Direct inquiry may reveal prior or current evidence of myocardial infarction, valvular disease, or congenital heart disease, whereas examination of the heart may suggest the presence of cardiac enlargement, murmurs, or a third heart sound. Although the history and physical examination may provide important clues about the nature of the underlying cardiac abnormality, identification of the structural abnormality leading to HF generally requires invasive or noninvasive imaging of the cardiac chambers or great vessels.

The single most useful diagnostic test in the evaluation of patients with HF is the two-dimensional echocardiogram coupled with Doppler flow studies. This test allows the physician to determine whether the primary abnormality is pericardial, myocardial, or valvular, and if myocardial, whether the dysfunction is primarily systolic or diastolic.

The primary functional information gained from the echocardiogram is the measurement of left ventricular ejection fraction; patients with an ejection fraction less than 40% are generally considered to have systolic dysfunction (10). In addition, the echocardiogram allows for the quantitative assessment of the dimensions, geometry, thickness, and regional motion of the right and left ventricles and the qualitative evaluation of the atria, pericardium, valves, and vascular structures. Such a comprehensive evaluation is important, since it is not uncommon for patients to have more than 1 cardiac abnormality that can cause or contribute to the development of HF.

Other tests may be used to provide information regarding the nature and severity of the cardiac abnormality. Radionuclide ventriculography can provide highly accurate measurements of global and regional function, but it is unable to directly assess valvular abnormalities or cardiac hypertrophy. Magnetic resonance imaging or computed tomography may be useful in evaluating ventricular mass, detecting right ventricular dysplasia or recognizing the presence of pericardial disease (11). Chest radiography can be used to estimate the degree of cardiac enlargement and pulmonary congestion or to detect the presence of pulmonary disease. A 12-lead electrocardiogram may demonstrate evidence of prior myocardial infarction, left ventricular hypertrophy, or a cardiac arrhythmia. However, because of their low sensitivity and specificity, neither the chest radiograph nor the electrocardiogram should form the primary basis for determining the specific cardiac abnormality responsible for the development of HF.

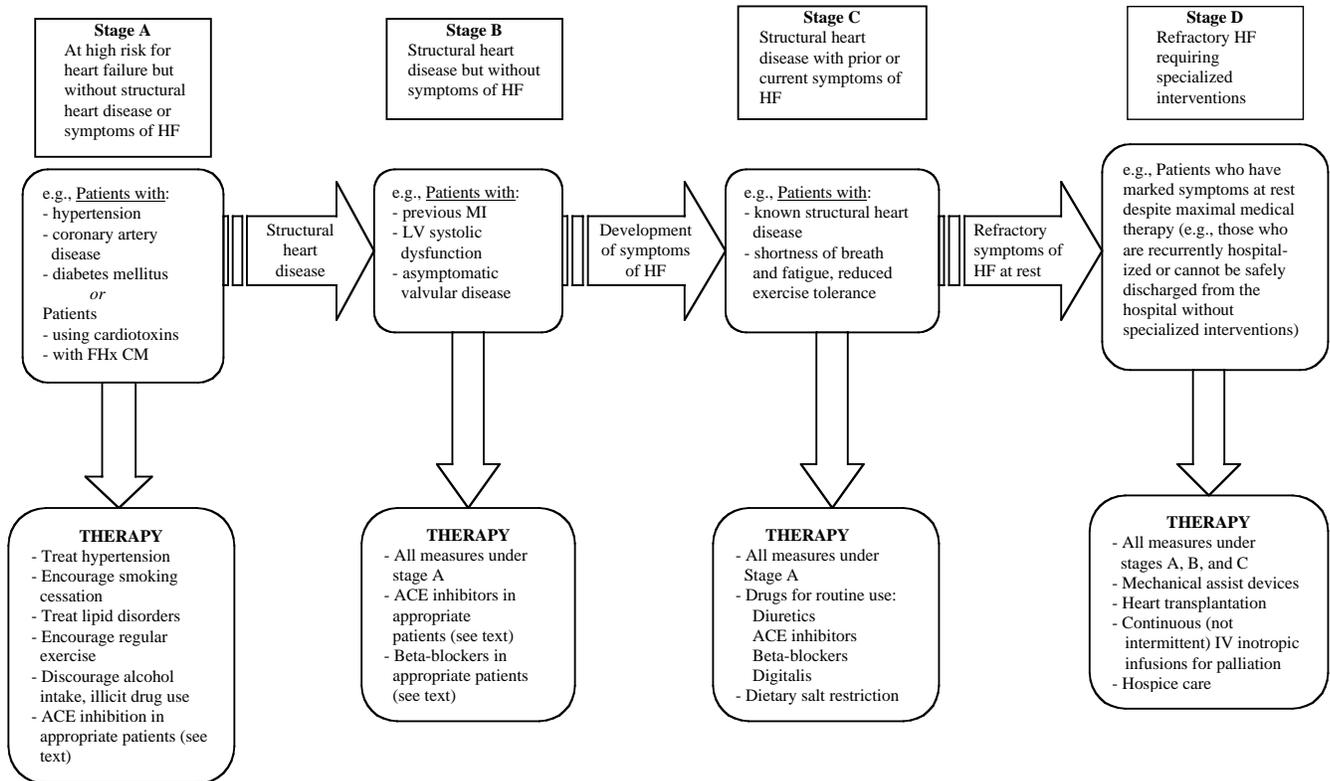


Figure 1. Stages in the evolution of heart failure and recommended therapy by stage. FHx CM indicates family history of cardiomyopathy; MI, myocardial infarction; LV, left ventricular; and IV, intravenous.

Recently, measurement of circulating levels of brain natriuretic peptide (BNP) has become available as a means of identifying patients with elevated left ventricular filling pressures who are likely to exhibit signs and symptoms of HF. The assessment of this peptide cannot reliably distinguish patients with systolic dysfunction from those with diastolic dysfunction. However, it has been widely investigated as a biochemical marker of morbidity and mortality in patients with known HF (12) and as an aid in differentiating dyspnea due to HF from dyspnea due to other causes in an emergency setting (13). The role of BNP measurement in the identification and management of patients with symptomatic or asymptomatic left ventricular dysfunction remains to be fully clarified.

3. Evaluation of Cause of Ventricular Dysfunction

Echocardiography and radionuclide ventriculography allow physicians to evaluate the presence and severity of left ventricular dysfunction but may provide little information about its cause. Identification of the disorder responsible for the depressed ejection fraction may be important, because some conditions that lead to left ventricular dysfunction are reversible or treatable, and efforts to identify a cause frequently allow the detection of co-existent conditions that may contribute to or exacerbate the severity of symptoms. However, it may not be possible to discern the cause of HF in many patients presenting with this syndrome, and in others, the underlying condition may not be amenable to treat-

ment. Hence, physicians should focus their efforts on diagnoses that have potential for improvement.

a. History and Physical Examination

Evaluation of potential causative factors begins with a thorough history and careful physical examination. Physicians should inquire about a history of hypertension; diabetes; hypercholesterolemia; coronary, valvular or peripheral vascular disease; rheumatic fever; chest irradiation; and exposure to cardiotoxic agents, including antineoplastic agents such as anthracyclines and trastuzumab. Patients should be questioned carefully about illicit drug use, amount of alcohol consumption, and exposure to sexually transmitted diseases. The history and physical evaluation should include specific consideration of noncardiac diseases such as collagen vascular disease, bacterial or parasitic infection, thyroid excess or deficiency, and pheochromocytoma. The physical examination should document specific signs of right and/or left HF with particular attention to the presence of elevated jugular venous pressure and a third heart sound since these have been shown to have prognostic significance (14).

A detailed family history should be obtained not only to determine whether there is a familial predisposition to atherosclerotic disease but also to identify relatives with cardiomyopathy, sudden unexplained death, conduction system disease, and skeletal myopathies. Recent studies suggest that as many as 20% of cases of idiopathic dilated cardiomyopathy may be familial, and polymorphisms in genes encoding

cardiac proteins may provide important prognostic information. However, the cost-effectiveness of family screening has not been established, and determination of the genotype of patients with familial cardiomyopathies or investigation of genetic polymorphisms is not routinely performed. Instead, an electrocardiogram and echocardiogram should be considered in first-degree relatives of patients with a dilated cardiomyopathy, and families with multiple cases of dilated cardiomyopathy should be referred to a center with expertise in genetic analysis and counseling.

b. Laboratory Testing

Laboratory testing may reveal the presence of disorders or conditions that can lead to or exacerbate HF. The initial evaluation of patients with HF should include a complete blood count, urinalysis, serum electrolytes (including calcium and magnesium), and blood lipids as well as tests of both renal and hepatic function, a chest radiograph, and a 12-lead electrocardiogram. Thyroid function tests (especially thyroid-stimulating hormone) should be measured, because both hyperthyroidism and hypothyroidism can be a primary or contributory cause of HF. Serum ferritin level and transferrin saturation may be useful to detect hemochromatosis; the allele for this disorder may be common, and affected patients may show improvement in left ventricular function after treatment with phlebotomy and chelating agents. Magnetic resonance imaging or biopsy of the heart or liver may be needed to confirm the presence of iron overload. Screening for human immunodeficiency virus (HIV) is recommended by some physicians and should be considered in patients who are at high risk, although the majority of patients who have cardiomyopathy due to HIV do not present with symptoms of HF until other clinical signs of HIV infection are apparent. Titers for other organisms are occasionally measured in patients with a recent onset of HF (especially in those with a recent viral syndrome), but the yield of such testing is low, and the therapeutic implications of a positive result are uncertain. Assays for connective tissue diseases and for pheochromocytoma should be performed if these diagnoses are suspected.

c. Evaluation of the Possibility of Coronary Artery Disease

Coronary artery disease is believed to be the underlying cause in approximately two thirds of patients with HF due to left ventricular systolic dysfunction (8). Therefore, it may be useful to define the presence, anatomic characteristics, and functional significance of coronary artery disease in selected patients who present with this syndrome.

PATIENTS WITH CORONARY ARTERY DISEASE AND ANGINA. Coronary artery bypass grafting has been shown to improve symptoms and survival in patients with HF and angina, although patients with severe symptoms of HF or markedly reduced ejection fractions were not included in these studies (15). Because revascularization is recommended in individu-

als with ischemic chest pain regardless of the degree of ischemia or viability, there would appear to be little role for noninvasive cardiac testing in such patients. Clinicians should proceed directly to coronary angiography in patients who have angina and impaired ventricular function (16).

PATIENTS WITH CORONARY ARTERY DISEASE AND NO ANGINA. Controlled trials have not addressed the issue of whether coronary revascularization can improve clinical outcomes in patients with HF who do not have angina. Nevertheless, the 1999 ACC/AHA Guidelines for Coronary Artery Bypass Graft Surgery (16) recommends revascularization in patients with a significant left main stenosis and in patients who have large areas of noninfarcted but hypoperfused and hypocontractile myocardium on noninvasive testing. Observational studies have shown that revascularization can favorably affect left ventricular function in some patients with impaired yet viable myocardium, but it is not clear how such patients should be identified because the sensitivity and specificity of an abnormal imaging test have not been validated in patients with HF. Additional studies are needed to determine whether the possibility of myocardial ischemia or viability should be routinely evaluated to assess the contribution of coronary artery disease in patients with HF due to left ventricular systolic dysfunction who do not have angina [see the ACC/AHA Guidelines for the Clinical Application of Echocardiography (10) and the ACC/AHA Guidelines for Clinical Use of Cardiac Radionuclide Imaging (11)].

PATIENTS IN WHOM THE POSSIBILITY OF CORONARY ARTERY DISEASE HAS NOT BEEN EVALUATED. Up to one third of patients with nonischemic cardiomyopathy complain of chest pain, which may resemble angina or may be atypical in nature. Because coronary revascularization would play a role in the management of these patients if their chest pain were related to the presence of coronary artery disease, coronary angiography is generally recommended in these circumstances to define the presence or absence of large-vessel coronary obstructions. Although many physicians perform noninvasive testing before coronary angiography in these patients, inhomogeneous nuclear images and abnormal wall-motion patterns are common in patients with a nonischemic cardiomyopathy. Hence, in most situations, clinicians should proceed directly to coronary angiography in patients who have HF and chest pain.

How should physicians evaluate patients with HF due to left ventricular dysfunction who do not have chest pain and who do not have a history of coronary artery disease? The use of coronary angiography appears reasonable in young patients to exclude the presence of congenital coronary anomalies. In older patients, however, efforts to detect the presence of coronary artery disease may not be worthwhile, because revascularization has not been shown to improve clinical outcomes in patients without angina (16). Nevertheless, the observations that revascularization might have a favorable effect on left ventricular function has led many experts to suggest that coronary artery disease should

be excluded whenever possible. Only coronary arteriography can reliably demonstrate or exclude the presence of obstructed coronary vessels, because perfusion deficits and segmental wall-motion abnormalities suggestive of coronary artery disease are commonly present in patients with a nonischemic cardiomyopathy.

In patients in whom coronary artery disease has been excluded previously as the cause of left ventricular dysfunction, repeated invasive or noninvasive assessment for ischemia is generally not indicated.

d. Evaluation of the Possibility of Myocardial Disease

One third of patients with HF due to left ventricular dysfunction have normal coronary arteries on coronary angiography, and in such individuals, myocardial disorders are responsible for the development of cardiomyopathy. Most patients with a cardiomyopathy have no identifiable causative factor (i.e., idiopathic dilated cardiomyopathy), but in some patients, the cardiomyopathy is related to a systemic disorder (e.g., hyperthyroidism, hemochromatosis, or hypocalcemia), to exposure to a cardiotoxic agent (alcohol, cocaine, anthracycline, or trastuzumab), or to the presence of myocardial inflammation or infiltration (which can be diagnosed by endomyocardial biopsy).

However, the overall usefulness of endomyocardial biopsy in the evaluation of patients with a cardiomyopathy of unknown cause is not clear (17). The biopsy has been advocated as a means of making the diagnosis of myocardial disorders that might not be suspected otherwise, but most patients with a nonischemic cardiomyopathy show nonspecific changes on biopsy (including hypertrophy, cell loss, and fibrosis), and biopsy findings (even when positive) frequently do not have a material effect on patient management (18). For example, the biopsy can detect inflammatory cell infiltrates attributed to viral myocarditis in some patients with acute or chronic HF, but many patients with acute myocarditis improve with supportive care without specific anti-viral or anti-inflammatory treatment, and the prognosis of chronic cardiomyopathy does not appear to be influenced by immunosuppression, whether or not histologic criteria for myocarditis are fulfilled (19). Similarly, the biopsy can be used to make a diagnosis of sarcoidosis and amyloidosis, but changes characteristic of these disorders are often missed on histological evaluation, and there is no evidence that treatment can favorably affect on the course of these diseases.

Hence, the weight of available evidence suggests a limited role for endomyocardial biopsy in the evaluation of patients with HF. Tissue obtained by biopsy can be used to make the diagnosis of hemochromatosis, endocardial fibroelastosis, and Loeffler's syndrome in patients in whom these disorders are suspected on clinical grounds. Biopsy tissue may also be used to assess the risk of continued anthracycline therapy in patients with cancer, especially when combined with imaging of ventricular function (20;21). Biopsies can confirm the presence of cardiac disorders that might disqualify patients for heart transplantation (e.g., amyloidosis). Finally, the

biopsy can be used to identify patients with giant-cell myocarditis, who generally progress rapidly to death and are unresponsive to treatment and who thus may be considered for immediate heart transplantation (22).

Thus, endomyocardial biopsy is not indicated in the routine evaluation of cardiomyopathy. Although the risk of a serious complication is less than 1%, biopsies should be performed only when there is a strong reason to believe that the results will have a meaningful effect on subsequent therapeutic decisions.

B. Ongoing Evaluation of Patients

Once the nature and cause of the structural abnormalities leading to the development of HF have been defined, physicians should focus on the clinical assessment of patients, both during the initial presentation and during subsequent visits. This clinical assessment should identify symptoms and their functional consequences and should evaluate the short- and long-term risks of disease progression and death whenever appropriate. This ongoing review of the patient's clinical status is critical to the appropriate selection and monitoring of treatments.

1. Assessment of Functional Capacity

During the initial and subsequent visits, physicians should inquire about the type, severity, and duration of symptoms that occur during activities of daily living and that may impair the patient's functional capacity. Questions regarding the ability to perform specific tasks may provide greater insight than general inquiries about what symptoms the patient is experiencing, because many patients curtail their activities to limit discomfort. Patients with modest limitations of activity should be asked about their participation in sports or their ability to perform strenuous exercise, whereas patients with substantial limitations of activity should be asked about their ability to get dressed without stopping, take a shower or bath, climb stairs, or perform specific routine household chores. A useful approach is to ask patients to describe activities that they would like to do but can no longer perform, because changes in the ability to perform specific tasks are generally related to important changes in clinical status or course. Ideally, these inquiries should be coupled with direct observations of the patient during a walk around the clinic or up the stairs.

A variety of approaches have been used to quantify the degree of functional limitation imposed by HF. The most widely used scale is the NYHA functional classification (22a), but this system is subject to considerable interobserver variability and is insensitive to important changes in exercise capacity. These limitations may be overcome by formal tests of exercise tolerance. Measurement of the distance that a patient can walk in 6 min has been shown to have prognostic significance, but serial changes in walking distance may not parallel changes in clinical status. Maximal exercise testing, as well as measurement of peak oxygen consumption, has been used to identify potential candidates for cardiac

transplantation, to determine disability, and to assist in the formulation of an exercise prescription, but its role in the general management of patients with HF has not been defined.

2. Assessment of Volume Status

It is critically important for physicians to evaluate the fluid or volume status of patients with HF during the initial visit and during each subsequent follow-up examination. This assessment plays a pivotal role in determining the need for diuretic therapy and in detecting sodium excesses or deficiencies that may limit the efficacy and decrease the tolerability of drugs used to treat HF. The physical examination is the primary step in evaluating the presence and severity of fluid retention in patients with HF. At each visit, physicians should record the patient's body weight and determine the degree of jugular venous distension and its response to abdominal pressure, the presence and severity of organ congestion (pulmonary rales and hepatomegaly), and the magnitude of peripheral edema in the legs, abdomen, presacral area, or scrotum.

The most reliable physical sign of volume overload is jugular venous distension (23-25). Right-sided pressures are elevated in nearly 80% of patients who have chronically elevated left-sided pressures due to systolic dysfunction (26). Most patients with peripheral edema should also be considered to have volume overload, although the possibility of noncardiac causes for edema may limit the utility of this sign in some patients. In contrast, most patients with chronic HF do not have pulmonary rales, even patients with end-stage disease who have markedly elevated left-sided filling pressures. The presence of rales generally reflects the rapidity of onset of HF rather than the degree of volume overload; hence, the finding of clear lung fields on physical examination in a patient with chronic HF should not suggest that fluid retention has been adequately treated. Of available measures, short-term *changes* in fluid status in the individual patient are most reliably gauged by measuring short-term *changes* in body weight. However, changes in body weight may be less reliable during long periods of follow-up, because many patients lose skeletal muscle mass and body fat as the disease advances, a syndrome known as cardiac cachexia.

The majority of patients with clinical evidence of volume overload do not exhibit hypoperfusion, even though cardiac performance may be severely depressed. Clinical signs of hypoperfusion become most apparent when cardiac output declines markedly and/or abruptly. Clues that suggest the presence of such a marked reduction in cardiac output include narrow pulse pressure, cool extremities, altered mentation, Cheynes-Stokes respiration, resting tachycardia, and a disproportionate elevation of blood urea nitrogen relative to serum creatinine. Renal dysfunction in HF is poorly understood and appears to be mediated by interactions between heart and kidney beyond those due primarily to depressed cardiac output (27).

3. Laboratory Assessment

Serum electrolytes and renal function should be monitored routinely in patients with HF. Of particular importance is the serial measurement of serum potassium concentration, because hypokalemia is a common adverse effect of treatment with diuretics and may increase the risk of digitalis toxicity, whereas hyperkalemia may complicate therapy with angiotensin converting enzyme (ACE) inhibitors and spironolactone. Worsening renal function may require adjustment of the doses of digoxin or diuretics.

Serial chest radiographs are not recommended in the management of chronic HF. Although the cardiothoracic ratio is commonly believed to reflect the cardiac dilatation that is characteristic of HF, enlargement of the cardiac silhouette primarily reflects changes in right ventricular volume rather than left ventricular function, because the right ventricle forms most of the border of dilated hearts on radiographs. Similarly, changes in the radiographic assessment of pulmonary vascular congestion are too insensitive to detect any but the most extreme changes in fluid status.

Once the patient is determined to have systolic dysfunction, there may be little to be learned from confirming its presence by noninvasive imaging at regular intervals. Although changes in ejection fraction or in chamber dimensions may have prognostic significance, it is not clear how detection of such changes should affect management, because treatment strategies should not necessarily be withdrawn or intensified if the ejection fraction increases or decreases. Repeat assessment of ejection fraction would appear to be justified primarily if the patient has had an important change in clinical status or has experienced or recovered from an event or received treatment that might have had a significant effect on cardiac function. The routine assessment of ejection fraction at regular intervals is not recommended.

Finally, the role of periodic invasive or noninvasive hemodynamic measurements in the management of HF remains uncertain. Most drugs used for the treatment of HF are prescribed on the basis of their ability to improve symptoms or survival rather than on their effect on hemodynamic variables, and the initial and target doses of these drugs are selected on the basis of experience in controlled trials and not based on the changes they may produce in cardiac output or pulmonary wedge pressure. Nevertheless, invasive hemodynamic measurements may assist in the determination of volume status and in distinguishing HF from other disorders such as pulmonary diseases and sepsis, that may cause circulatory instability. Measurements of cardiac output and pulmonary wedge pressure through a pulmonary artery catheter have also been used in patients with end-stage HF to assess pulmonary vascular resistance, a determinant of eligibility for heart transplantation. Although hemodynamic measurements can also be performed by noninvasive methods such as transthoracic bioimpedance, routine use of this technology cannot be recommended at the present time because the accuracy of bioelectrical parameters has not been defined in patients with chronic HF and it has not been shown to be

more valuable than routine tests, including the physical examination. Moreover, it is not clear whether serial noninvasive hemodynamic measurements can be used to gauge the efficacy of treatment or to identify patients most likely to deteriorate symptomatically during long-term follow-up.

4. Assessment of Prognosis

Although both physicians and patients may be interested in defining the prognosis of an individual patient with HF, the likelihood of survival can be determined reliably only in populations and not in individuals. Patients may describe a need to know their prognosis in order to make plans, but the wide range of uncertainty rarely facilitates planning. Once HF is advanced, physicians may wish to estimate survival to guide the timing of transplantation or other treatments that are reserved for patients with very severe disease. For patients with end-stage HF, an estimated survival less than 6 months increases the options for hospice care, although such predictions are inherently unreliable.

For most patients, measurements of clinical status and functional capacity have generally provided the most useful prognostic information. In patients with no or mild symptoms of HF, estimates of survival can be further refined by the measurement of left ventricular ejection fraction, but the utility of this variable diminishes once its value declines to less than 25%. As the disease advances, measurements of serum sodium concentration and renal function become increasingly important in defining prognosis. Although elevated circulating levels of neurohormonal factors have also been associated with high mortality rates, the routine assessment of norepinephrine or endothelin cannot be recommended because the amount of incremental information provided by these tests has not been shown to add significantly to clinical assessment. Similarly, routine use of Holter monitoring or signal-averaged electrocardiography has not been shown to provide incremental value either in assessing prognosis or in guiding treatment. As noted elsewhere in these guidelines, the role of measurement of BNP is currently being investigated.

5. Brain Natriuretic Peptide

Plasma BNP is a 32-amino acid polypeptide that contains a 17-amino acid ring structure common to all natriuretic peptides. The cardiac ventricles are the major source of plasma BNP. This circulating peptide has recently emerged as a potentially useful marker that may aid in the diagnosis of congestive HF (28). In general, plasma BNP levels correlate positively with the degree of left ventricular dysfunction (28), but they are sensitive to other biological factors such as age, sex, and diastolic dysfunction. A plasma BNP level greater than 100 pg per mL supports a diagnosis of abnormal ventricular function or symptomatic HF (28). Clinical experience with this diagnostic marker is very limited, but it may have utility in the urgent-care setting, where it has been used to differentiate dyspnea due to HF from pulmonary disease with acceptable sensitivity and specificity (13). It may also

be useful in managing patients with HF (29;30), but more research will be necessary to determine its role in both diagnosis and management.

Recommendations for the Evaluation of Patients With HF

Class I

1. **Thorough history and physical examination to identify cardiac and noncardiac disorders that might lead to the development of HF or accelerate the progression of HF. (Level of Evidence: C)**
2. **Initial and ongoing assessment of a patient's ability to perform routine and desired activities of daily living. (Level of Evidence: C)**
3. **Initial and ongoing assessment of volume status. (Level of Evidence: C)**
4. **Initial measurement of complete blood count, urinalysis, serum electrolytes (including calcium and magnesium), blood urea nitrogen, serum creatinine, blood glucose, liver function tests, and thyroid-stimulating hormone. (Level of Evidence: C)**
5. **Serial monitoring of serum electrolytes and renal function. (Level of Evidence: C)**
6. **Initial 12-lead electrocardiogram and chest radiograph. (Level of Evidence: C)**
7. **Initial 2-dimensional echocardiography with Doppler or radionuclide ventriculography to assess left ventricular systolic function. (Level of Evidence: C)**
8. **Cardiac catheterization with coronary arteriography in patients with angina who are candidates for revascularization. (Level of Evidence: B)**

Class IIa

1. **Cardiac catheterization with coronary arteriography in patients with chest pain who have not had evaluation of their coronary anatomy and who have no contraindications to coronary revascularization. (Level of Evidence: C)**
2. **Cardiac catheterization with coronary arteriography in patients with known or suspected coronary artery disease but without angina who are candidates for revascularization. (Level of Evidence: C)**
3. **Noninvasive imaging to detect ischemia and viability in patients with known coronary artery disease and no angina who are being considered for revascularization. (Level of Evidence: C)**
4. **Maximal exercise testing with measurement of respiratory gas exchange and/or blood oxygen saturation to help determine whether HF is the cause of exercise limitation when the contribution of HF is uncertain. (Level of Evidence: C)**
5. **Maximal exercise testing with measurement of respiratory gas exchange to identify high-risk patients who are candidates for cardiac transplantation or other advanced treatments. (Level of Evidence: B)**

6. **Echocardiography in asymptomatic first-degree relatives of patients with idiopathic dilated cardiomyopathy. (Level of Evidence: C)**
7. **Repeat measurement of ejection fraction in patients who have had a change in clinical status or who have experienced or recovered from a clinical event or received treatment that might have had a significant effect on cardiac function. (Level of Evidence: C)**
8. **Screening for hemochromatosis. (Level of Evidence: C)**
9. **Measurement of serum antinuclear antibody, rheumatoid factor, urinary vanillylmandelic acid, and metanephrines in selected patients. (Level of Evidence: C)**

Class IIb

1. **Noninvasive imaging to define the likelihood of coronary artery disease in patients with left ventricular dysfunction. (Level of Evidence: C)**
2. **Maximal exercise testing with measurement of respiratory gas exchange to facilitate prescription of an appropriate exercise program. (Level of Evidence: C)**
3. **Endomyocardial biopsy in patients in whom an inflammatory or infiltrative disorder of the heart is suspected. (Level of Evidence: C)**
4. **Assessment of HIV status. (Level of Evidence: C)**

Class III

1. **Endomyocardial biopsy in the routine evaluation of patients with HF. (Level of Evidence: C)**
2. **Routine Holter monitoring or signal-averaged electrocardiography. (Level of Evidence: C)**
3. **Repeat coronary arteriography or noninvasive testing for ischemia in patients for whom coronary artery disease has previously been excluded as the cause of left ventricular dysfunction. (Level of Evidence: C)**
4. **Routine measurement of circulating levels of norepinephrine or endothelin. (Level of Evidence: C)**

IV. THERAPY

A. Patients at High Risk for Developing Left Ventricular Dysfunction (Stage A)

Many conditions or behaviors that are associated with an increased risk of HF can be identified *before* patients show any evidence of structural heart disease. Because early modification of these factors can often reduce the risk of HF, working with patients with these risk factors provides the earliest opportunity to reduce the impact of HF on public and individual health.

1. Control of Risk

a. Treatment of Hypertension

Elevated levels of either systolic or diastolic blood pressure are a major risk factor for the development of HF (31;32), and long-term treatment of both systolic and diastolic hyper-

tension has been shown to reduce the risk of HF (33;34). Physicians should lower both systolic and diastolic blood pressure in accordance with the recommendations provided in published guidelines (35); target levels of blood pressure are lower in patients with associated major cardiovascular risk factors (e.g., diabetes) (36;37). An appropriate antihypertensive regimen frequently consists of several drugs used in combination. When such a regimen is devised, drugs that are useful for the treatment of both hypertension and HF are preferred (e.g., diuretics, ACE inhibitors, and beta-blockers).

b. Treatment of Diabetes

The presence of diabetes markedly increases the likelihood of HF in patients without structural heart disease (38) and adversely affects the outcomes of patients with established HF (39;40). Physicians should make every effort to control hyperglycemia, although such control has not yet been shown to reduce the subsequent risk of HF. In addition, ACE inhibitors can prevent the development of end-organ disease and the occurrence of clinical events in diabetic patients even in those who do not have hypertension (41;42). Long-term treatment with several ACE inhibitors has been shown to decrease the risk of renal disease in diabetic patients (43;44), and prolonged therapy with the ACE inhibitor ramipril has been shown to lower the likelihood of cardiovascular death, myocardial infarction, and HF (41).

c. Management of Atherosclerotic Disease

Patients with known atherosclerotic disease (e.g., of the coronary, cerebral, or peripheral blood vessels) are likely to develop HF, and physicians should seek to control vascular risk factors in such patients. Treatment of hyperlipidemia (in accordance with published guidelines) has been shown to reduce the likelihood of death and of HF in patients with a history of a myocardial infarction (45). In one large-scale trial, long-term treatment with an ACE inhibitor decreased the risk of cardiovascular death, myocardial infarction, and HF in patients with established vascular disease, even when treatment was started before the development of left ventricular systolic dysfunction (41).

d. Control of Conditions That May Cause Cardiac Injury

Many therapeutic and recreational agents can exert important cardiotoxic effects, and patients should be strongly advised about the hazards of smoking, as well as the use of alcohol, cocaine, and other illicit drugs. Several interventions used in the treatment of cancer can injure the heart and lead to the development of HF, even in patients with no other cardiovascular risk factors. Such treatments include ionizing radiation that involves the mediastinum (46) and chemotherapeutic agents such as anthracyclines or trastuzumab (47;48). Patients who take trastuzumab in combination with anthracyclines are at particular risk of HF. Heart failure may occur

years after initial exposure to anthracyclines or mediastinal radiotherapy.

Physicians should treat other diseases that may adversely affect the heart, especially thyroid disorders. In addition, because prolonged tachycardia may lead to a cardiomyopathy in otherwise normal individuals (49;50), every effort should be made to suppress the occurrence of or control the ventricular response to supraventricular tachyarrhythmias (see Section V).

e. Other Measures

There is no evidence that control of dietary sodium or participation in regular exercise can prevent the development of HF in normal individuals or in patients at risk, although these efforts may have other health benefits and may enhance a general sense of well-being. There is also no evidence that routine use of nutritional supplements can prevent dysfunction of or injury to the heart.

2. Early Detection of Ventricular Dysfunction

It is not clear whether patients at high risk should be evaluated periodically for the occurrence of ventricular dysfunction in the absence of symptoms or a history of cardiac injury. Noninvasive evaluation of the large numbers of patients at risk would be likely to detect very few patients with systolic dysfunction, and the benefits of early detection of left ventricular dysfunction through such screening programs have not been established. Nevertheless, it appears reasonable to perform echocardiographic evaluation in selected patients without apparent structural heart disease who are at very high risk of a cardiomyopathy (e.g., those with a strong family history of cardiomyopathy or those receiving cardiotoxic interventions) (51;52). Routine periodic assessment of left ventricular function in other patients is not recommended.

Recommendations for Patients at High Risk of Developing HF (Stage A)

Class I

- 1. Control of systolic and diastolic hypertension in accordance with recommended guidelines. (Level of Evidence: A)**
- 2. Treatment of lipid disorders, in accordance with recommended guidelines. (Level of Evidence: B)**
- 3. Avoidance of patient behaviors that may increase the risk of HF (e.g., smoking, alcohol consumption, and illicit drug use). (Level of Evidence: C)**
- 4. ACE inhibition in patients with a history of atherosclerotic vascular disease, diabetes mellitus, or hypertension and associated cardiovascular risk factors. (Level of Evidence: B)**

- 5. Control of ventricular rate in patients with supraventricular tachyarrhythmias. (Level of Evidence: B)**
- 6. Treatment of thyroid disorders. (Level of Evidence: C)**
- 7. Periodic evaluation for signs and symptoms of HF. (Level of Evidence: C)**

Class IIa

Noninvasive evaluation of left ventricular function in patients with a strong family history of cardiomyopathy or in those receiving cardiotoxic interventions. (Level of Evidence: C)

Class III

- 1. Exercise to prevent the development of HF. (Level of Evidence: C)**
- 2. Reduction of dietary salt beyond that which is prudent for healthy individuals in patients without hypertension or fluid retention. (Level of Evidence: C)**
- 3. Routine testing to detect left ventricular dysfunction in patients without signs or symptoms of HF or evidence of structural heart disease. (Level of Evidence: C)**
- 4. Routine use of nutritional supplements to prevent the development of structural heart disease. (Level of Evidence: C).**

B. Patients With Left Ventricular Dysfunction Who Have Not Developed Symptoms (Stage B)

Patients without symptoms but who have had a myocardial infarction or have evidence of left ventricular dysfunction are at considerable risk of developing HF (45;53). In such patients, HF can be prevented by reducing the risk of additional injury and by retarding the evolution and progression of left ventricular dysfunction. Appropriate measures include those listed as class I recommendations for patients in Stage A (also see Section V).

However, as is the case with patients who have no structural heart disease, there is no evidence that control of dietary sodium, participation in regular exercise, or use of nutritional supplements can prevent the development of HF in patients with a recent or remote myocardial infarction with or without left ventricular systolic dysfunction.

1. Prevention of Cardiovascular Events

a. Patients With an Acute Myocardial Infarction

In patients who are experiencing an acute myocardial infarction, the infusion of a thrombolytic agent or the use of percutaneous coronary intervention can decrease the risk of developing HF (54), and these interventions can reduce the risk of death, especially in patients with a prior myocardial injury (55;56). Patients with an acute infarction also benefit from the administration of an ACE inhibitor or a beta-blocker (or a combination of both drugs), which can decrease the risk of reinfarction or death when initiated soon after the ischemic event, especially in patients whose course is com-

plicated by HF (57-62). Combined neurohormonal blockade (ACE inhibitor and a beta-blocker) may produce complementary benefits (63).

b. Patients With a History of Myocardial Infarction But Preserved Left Ventricular Function

Both hypertension and hyperlipidemia should be treated vigorously in patients with a history of myocardial infarction, because the benefits of treating these coronary risk factors are particularly marked in patients with a prior ischemic event (33;34;45). Patients with a recent myocardial infarction should also receive treatment with ACE inhibitors and beta-blockers (57;58;61-63), which have been shown to reduce the risk of death when initiated days or weeks after an ischemic cardiac event. Evidence from a large-scale study indicates that prolonged therapy with an ACE inhibitor can also reduce the risk of a major cardiovascular event, even when treatment is initiated months or years after myocardial infarction (41).

c. Patients With Chronic Left Ventricular Systolic Dysfunction But No Symptoms

Long-term treatment with an ACE inhibitor has been shown to delay the onset of symptoms and decrease the combined risk of death and hospitalization for HF in asymptomatic patients with left ventricular systolic dysfunction, whether due to a remote ischemic injury or to a nonischemic cardiomyopathy (53). Furthermore, although controlled clinical trials are lacking, the use of beta-blockers in patients with a low ejection fraction and no symptoms (especially those with coronary artery disease) is also warranted (60;63).

In contrast, there are no data to recommend the use of digoxin in patients with asymptomatic LV dysfunction. Because the only reason to treat such patients is to prevent the progression of HF, and because digoxin has minimal effect on disease progression in symptomatic patients (64), it is unlikely that the drug would be beneficial in those with no symptoms.

Physicians should pay particular attention to patients whose cardiomyopathy is associated with a rapid arrhythmia of supraventricular origin (e.g., atrial flutter or atrial fibrillation). Although physicians frequently consider such tachycardias to be the result of an impairment of ventricular function, these rhythm disorders may lead to or exacerbate the development of a cardiomyopathy (49;50). Therefore, in patients with a depressed left ventricular ejection fraction, every effort should be made to control the ventricular response to these tachyarrhythmias or to restore sinus rhythm (see Section V).

d. Patients With Severe Valvular Disease But No Symptoms

Patients with severe aortic or mitral valve stenosis or regurgitation should be considered for valve replacement surgery, even when ventricular function is impaired (65-67). Those

with severe aortic regurgitation who are deemed poor candidates for surgery may be considered for long-term treatment with a systemic vasodilator drug. Several studies (68;69) have suggested that prolonged therapy with hydralazine and nifedipine in patients with severe aortic regurgitation and preserved left ventricular function might act to minimize structural changes in the ventricle and thereby possibly delay the need for surgical intervention. However, these drugs are often poorly tolerated in this setting, and no trial has shown that these vasodilators can reduce the risk of HF or death [see ACC/AHA Guidelines for the Management of Patients with Valvular Heart Disease (7)]. There are no long-term studies of vasodilator therapy in patients with severe asymptomatic mitral regurgitation.

2. Early Detection of HF

The symptoms and signs of HF are often difficult to identify, because they are frequently confused with other disorders or are attributed to aging, obesity, or lack of conditioning. Limitations of exercise tolerance can occur so gradually that patients may adapt their lifestyles (consciously or subconsciously) to minimize symptoms and thus fail to report them to physicians. Hence, patients at risk should be advised to inform their health care providers about limitations of exercise tolerance or unexplained fatigue, and physicians should intensify their vigilance for the signs and symptoms of HF in such individuals.

Recommendations for Patients With Asymptomatic Left Ventricular Systolic Dysfunction (Stage B)

Class I

- 1. ACE inhibition in patients with a recent or remote history of myocardial infarction regardless of ejection fraction. (Level of Evidence: A)**
- 2. ACE inhibition in patients with a reduced ejection fraction, whether or not they have experienced a myocardial infarction. (Level of Evidence: B)**
- 3. Beta-blockade in patients with a recent myocardial infarction regardless of ejection fraction. (Level of Evidence: A)**
- 4. Beta-blockade in patients with a reduced ejection fraction, whether or not they have experienced a myocardial infarction. (Level of Evidence: B)**
- 5. Valve replacement or repair for patients with hemodynamically significant valvular stenosis or regurgitation. (Level of Evidence: B)**
- 6. Regular evaluation for signs and symptoms of HF. (Level of Evidence: C)**
- 7. Measures listed as Class I recommendations for patients in Stage A. (Levels of Evidence: A, B, and C as appropriate).**

Class IIb

- Long-term treatment with systemic vasodilators in patients with severe aortic regurgitation. (Level of Evidence: B)**

Class III

1. **Treatment with digoxin in patients with left ventricular dysfunction who are in sinus rhythm. (Level of Evidence: C)**
2. **Reduction of dietary salt beyond that which is prudent for healthy individuals in patients without hypertension or fluid retention. (Level of Evidence: C)**
3. **Exercise to prevent the development of HF. (Level of Evidence: C)**
4. **Routine use of nutritional supplements to treat structural heart disease or prevent the development of symptoms of HF. (Level of Evidence: C)**

C. Patients With Left Ventricular Dysfunction With Current or Prior Symptoms (Stage C)

1. 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 (also see Section V). 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 decompensation 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 (70-73).

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

1. Antiarrhythmic agents (74) can exert important cardiodepressant and proarrhythmic effects. Of available agents, only amiodarone has been shown not to adversely affect survival.
2. Calcium channel blockers (75) can lead to worsening HF and have been associated with an increased risk of cardiovascular events. Of available agents, only amlodipine has been shown not to adversely affect survival.
3. Nonsteroidal anti-inflammatory drugs (76) can cause sodium retention and peripheral vasoconstriction and can attenuate the efficacy, and enhance the toxicity, of diuretics and ACE inhibitors (77-79).

Patients with HF should be monitored closely 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 (80). Activation of both the sympathetic nervous system and renin-angiotensin systems can lead to hypokalemia (81;82), and most drugs used for the treatment of HF can alter serum potassium (83). Even modest decreases in serum potassium can increase the

risks of using digitalis and antiarrhythmic drugs (80;84), and even modest increases in serum potassium may prevent the utilization of treatments known to prolong life (85). Hence, many experts believe that serum potassium concentrations in the range of 3.5 to 3.8 mmol per L or 5.2 to 5.5 mmol per L should be avoided in patients with HF, even though such measurements may be in the range of normal values for many laboratories. In some patients, correction of potassium deficits may require supplementation of magnesium as well as potassium (86). In others (particularly those taking ACE inhibitors alone or in combination with spironolactone), 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. Noncompliance 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 noncompliance and lead to the detection of changes in body weight or clinical status early enough to allow the patient or a health care 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 (87-90).

2. Drugs Recommended for Routine Use

Most patients with HF should be routinely managed with a combination of 4 types of drugs: a diuretic, an ACE inhibitor, a beta-adrenergic blocker, and (usually) digitalis (91) (Table 2). 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 ACE inhibitor 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 may be initiated at any time to reduce symptoms and enhance exercise tolerance.

a. 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-

Table 2. Drugs Commonly Used for Treatment of Chronic Heart Failure

Drug	Initial Dose	Maximum Dose
Loop diuretics*		
Bumetanide	0.5 to 1.0 mg once or twice daily	Titrate to achieve dry weight (up to 10 mg daily)
Furosemide	20 to 40 mg once or twice daily	Titrate to achieve dry weight (up to 400 mg daily)
Torsemide	10 to 20 mg once or twice daily	Titrate to achieve dry weight (up to 200 mg daily)
ACE inhibitors		
Captopril	6.25 mg 3 times daily	50 mg 3 times daily
Enalapril	2.5 mg twice daily	10 to 20 mg twice daily
Fosinopril	5 to 10 mg once daily	40 mg once daily
Lisinopril	2.5 to 5.0 mg once daily	20 to 40 mg once daily
Quinapril	10 mg twice daily	40 mg twice daily
Ramipril	1.25 to 2.5 mg once daily	10 mg once daily
Beta-receptor blockers		
Bisoprolol	1.25 mg once daily	10 mg once daily
Carvedilol	3.125 mg twice daily	25 mg twice daily; 50 mg twice daily for patients more than 85 kg
Metoprolol tartrate	6.25 mg twice daily	75 mg twice daily
Metoprolol succinate extended release+	12.5 to 25 mg daily	200 mg once daily
Digitalis glycosides		
Digoxin	0.125 to 0.25 mg once daily	0.125 to 0.25 mg once daily

ACE indicates angiotensin converting enzyme.

*Thiazide diuretics are not listed in this table but may be appropriate for patients with mild heart failure or associated hypertension or as a second diuretic in patients refractory to loop diuretics alone.

+Referred to in some publications as metoprolol CR/XL.

sparing agents (e.g., spironolactone) act in the distal portion of the tubule (92;93). These 2 classes of diuretics differ in their pharmacologic 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 moderately impaired renal function (creatinine clearance less than 30 mL per min). Consequently, the loop diuretics have emerged as the preferred diuretic agents for use in most patients with HF.

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 (94;95). 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 was 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 (96-98). 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, physicians 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, ACE inhibitors, or beta-blockers may require weeks or months to become apparent (99;100).

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 ACE inhibitors can enhance urinary sodium excretion (101;102), few patients with HF can maintain sodium balance without the use of diuretic drugs. Attempts to substitute ACE inhibitors for diuretics can lead to pulmonary and peripheral congestion (98).

3. Diuretics should not be used alone in the treatment of 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 (98). The risk of clinical decompensation can be reduced, however, when diuretics are combined with digoxin, an ACE inhibitor, and a beta-blocker (103).

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 cause fluid retention, which can diminish the response to ACE inhibitors and increase the risk of treatment with beta-blockers (104). Conversely, the use of inappropriately high doses of diuretics will lead to volume contraction, which can increase the risk of hypotension with ACE inhibitors and vasodilators (105;106) and the risk of renal insufficiency with ACE inhibitors and angiotensin II receptor antagonists (107). 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 ACE inhibitor and a beta-blocker (and usually digoxin). Few patients with HF will be able to maintain dry weight without the use of diuretics.

Initiation and maintenance. The most commonly used loop diuretic for the treatment of HF is furosemide, but some patients respond favorably to newer agents in this category (e.g., torsemide) because of their superior absorption (108). One study has suggested that torsemide may reduce the risk of worsening HF more effectively than furosemide (109), but this issue remains controversial.

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 of diuretic administration may be required to maintain an active diuresis and sustain the loss of weight. The ultimate goal of treatment is to eliminate physical signs of fluid retention, either by restoring jugular venous pressures toward normal or by eliminating the presence of edema, or both. Diuretics are generally combined with moderate dietary sodium restriction (less than 3 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. 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 (104).

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 should be adjusted periodically. In many cases, this adjustment can be accomplished by having the patient record his or her weight each day and allowing the patient to make changes in dose 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 (92;93). 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 may be impaired by a decline in renal perfusion and function (110-112). Consequently, the clinical progres-

sion 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 cyclooxygenase-2 inhibitors) (77;78;113) or have a significant impairment of renal function or perfusion (108). Diuretic resistance can generally be overcome by the intravenous administration of diuretics (including the use of continuous infusions) (114), the use of 2 or more diuretics in combination (e.g., furosemide and metolazone) (115-118), or the use of diuretics together with drugs that increase renal blood flow (e.g., positive inotropic agents) (118).

Risks of treatment. The principal adverse effects of diuretics include electrolyte 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 (119). 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 (93). Potassium deficits can be corrected by the short-term use of potassium supplements, or if severe, by the addition of magnesium supplements (120). Concomitant administration of ACE inhibitors 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 is frequently not needed and may be deleterious.

Excessive use of diuretics can decrease blood pressure and impair renal function and exercise tolerance (105-107;121), 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. If there are signs of fluid retention, hypotension and azotemia are likely to reflect worsening HF and a decline in effective peripheral perfusion. Such patients should be managed by maintaining the dose of diuretic and improving end-organ perfusion (118).

b. ACE Inhibitors

Angiotensin converting-enzyme inhibitors interfere with the renin-angiotensin system by inhibiting the enzyme responsible for the conversion of angiotensin I to angiotensin II, but it is not clear whether the effects of ACE inhibitors can be

explained solely by the suppression of angiotensin II. ACE inhibition not only interferes with the renin-angiotensin system but also enhances the action of kinins and augments kinin-mediated prostaglandin (122-124), and kinin potentiation may be as important as angiotensin suppression in mediating the effects of ACE inhibitors. In experimental models of HF, ACE inhibitors modify cardiac remodeling more favorably than angiotensin II receptor antagonists (125-128), and this advantage of ACE inhibitors is abolished by the co-administration of kinin (125;127). In the clinical setting, ACE inhibitors produce long-term benefits even though circulating levels of angiotensin II are not suppressed during prolonged treatment (129), and these benefits may be attenuated by the co-administration of aspirin (130-132), which can block kinin-mediated prostaglandin synthesis.

EFFECT OF ACE INHIBITORS IN THE MANAGEMENT OF HF. ACE inhibitors have been evaluated in more than 7000 patients with HF who participated in more than 30 placebo-controlled clinical trials (133). All of these trials enrolled patients with systolic dysfunction (ejection fraction less than 0.35 to 0.40) 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 left ventricular dysfunction. However, patients with preserved systolic function, low blood pressure (less 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 ACE inhibitors can alleviate symptoms, improve clinical status, and enhance the overall sense of well-being of patients with HF (134-142). In addition, ACE inhibitors can reduce the risk of death as well as the combined risk of death or hospitalization (143-145). 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.* ACE inhibitors should be prescribed to all patients with HF due to left ventricular systolic dysfunction 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 ACE inhibitor should not be delayed until the patient is found to be resistant to treatment with other drugs.

In general, ACE inhibitors are used together with a beta-blocker (and usually with digitalis). ACE 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 (98). ACE inhibitors should be preferred over the use of angiotensin II receptor antagonists or direct-acting vasodilators (e.g., a combination of hydralazine and isosorbide dinitrate (144;146).

Patients should not be given an ACE inhibitor 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 ACE inhibitor 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 L). Finally, treatment with an ACE inhibitor should not be initiated in hypotensive patients who are at immediate risk of cardiogenic shock. Such patients should first receive appropriate 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 supporting an effect of ACE inhibitors on the survival of patients with HF is derived from experience with enalapril, the available data suggest that there are no differences among available ACE inhibitors in their effects on symptoms or survival (133). 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 ACE inhibitors in any clinical aspect of HF. Nevertheless, in selecting among ACE inhibitors, it is recommended to give preference to ACE inhibitors that have been shown to reduce morbidity and mortality in clinical trials (captopril, enalapril, lisinopril, and ramipril), 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 ACE inhibitors that have not been shown to be effective in large-scale studies.

Treatment with an ACE inhibitor should be initiated at very low doses, 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, or azotemia or in those taking potassium supplements. Because fluid retention can blunt the therapeutic effects and fluid depletion can potentiate the adverse effects of ACE (104;107), physicians should ensure that patients are being given appropriate doses of diuretics before and during treatment with these drugs. In general, adverse effects that subside spontaneously or after changes in background medications should not alter the schedule of dose increments, but physicians should delay any planned increments in dose if side effects persist or have not responded adequately to changes in background medication. Most patients (85% to 90%) with HF can tolerate short- and long-term therapy with these drugs (143-145).

What dose of an ACE inhibitor should physicians try to achieve in patients with HF? In controlled clinical trials that were designed to evaluate survival, the dose of the ACE inhibitor was not determined by a patient's therapeutic response but was increased until a target dose was reached (143-145). 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 ACE inhibitors, 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 ACE inhibitors were generally used as background therapy. In a large, multicenter trial, high doses of an ACE inhibitor were better than low doses in reducing the risk of hospitalization, but the 2 doses had similar effects on symptoms and mortality (147). These findings suggest that physicians should attempt to prescribe doses of an ACE inhibitor that have been shown to reduce the risk of cardiovascular events in clinical trials, and if these target doses of an ACE inhibitor cannot be used or are poorly tolerated, lower doses should be used with the expectation that there are likely to be only small differences in efficacy between low and high doses.

Once the drug has been titrated to the appropriate dose, patients can generally be maintained on long-term therapy with an ACE inhibitor with little difficulty. Although symptoms may improve in some patients within the first 48 h of therapy with an ACE inhibitor, the clinical responses to these drugs are generally delayed and may require several weeks, months, or more to become apparent (99;134). Even if symptoms do not improve, long-term treatment with an ACE inhibitor should be maintained to reduce the risk of death or hospitalization. Abrupt withdrawal of treatment with an ACE inhibitor can lead to clinical deterioration and should be avoided (148) 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 ACE inhibitor, because changes in salt and water balance can exaggerate or attenuate the cardiovascular and renal effects of treatment (104;107). Fluid retention can minimize the symptomatic benefits of ACE inhibition, whereas fluid loss increases the risk of hypotension and azotemia. The use of an ACE inhibitor 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 ACE inhibitors in patients with HF and should be avoided (79;81).

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 (149;150). As a result, in such patients (particularly those who are responding poorly to diuretic drugs), it may be prudent to interrupt treatment with the ACE inhibitor 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

studies, aspirin can attenuate the hemodynamic actions of ACE inhibitors in patients with HF (130), an effect not seen with nonaspirin anti-platelet agents (e.g., clopidogrel) (151). In several multicenter trials, concomitant use of aspirin was associated with a diminution of the effect of ACE inhibitors on survival and on cardiovascular morbidity (131;132). Nevertheless, many physicians believe that the data supporting the existence of an adverse interaction between aspirin and ACE inhibitors are not sufficiently compelling to justify altering the current practice of prescribing the 2 agents together. In contrast, other physicians would consider the withdrawal of aspirin (because there are no data indicating it can reduce the risk of ischemic events in patients with HF) (152;153) or the use of an alternative antiplatelet agent such as clopidogrel, which does not interact with ACE inhibitors and which may have superior effects in preventing ischemic events (151;154).

Risks of treatment. Most of the adverse reactions of ACE inhibitors 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 ACE inhibitor, 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 L) (155).

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. 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 (156), and ACE inhibition may cause functional renal insufficiency (107). 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) (157). A significant increase in serum creatinine (e.g., greater than 0.3 mg per dl) with the use of ACE inhibitors is observed in 15% to 30% of patients with severe HF (158), but in only 5% to 15% of patients with mild to moderate symptoms (159). The risks are substantially greater if patients have bilateral renal artery stenosis or are taking non-steroidal anti-inflammatory drugs (78;81;160). 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 ACE inhibitor (107). 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 ACE inhibitor.

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, especially if they have diabetes mellitus (161).

Adverse Effects Related to Kinin Potentiation

1. Cough. Cough related to the use of ACE inhibitors is the most common reason for the withdrawal of long-term treatment with these drugs (162); the frequency of cough is approximately 5% to 10% in white patients of European descent and rises to nearly 50% in Chinese patients (163). 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 ACE inhibitor should be implicated only after these have been excluded. Demonstration that the cough disappears after drug withdrawal and recurs after rechallenge with another ACE inhibitor strongly suggests that ACE inhibition is the cause of the cough. Because of the long-term benefits of ACE inhibitors, 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 ACE inhibitor and the use of alternative medications (e.g., an angiotensin II receptor antagonist).

2. Angioedema. Angioedema occurs in fewer than 1% of patents taking an ACE inhibitor but is more frequent in blacks. Because its occurrence may be life-threatening, the clinical suspicion of this reaction justifies subsequent avoidance of all ACE inhibitors for the lifetime of the patient (162). ACE inhibitors should not be initiated in any patient with a history of angioedema.

c. Beta-Adrenergic Receptor Blockers

Beta-blockers act principally to inhibit the adverse effects of the sympathetic nervous system in patients with HF. 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 (164) and by impairing sodium excretion by the kidneys (165). Norepinephrine can also induce cardiac hypertrophy but restrict the ability of the coronary arteries to supply blood to the thickened ventricular wall, leading to myocardial ischemia (166-168). 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 (82;169-171). 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 (172). These deleterious effects are mediated through actions on alpha-1-, beta-1-, and beta-2-adrenergic receptors (82;164-172).

Beta-blockers that have been shown to be effective in the treatment of HF include those that selectively block beta-1-receptors (e.g., bisoprolol and metoprolol) and those that block alpha-1, beta-1-, and beta-2-adrenergic receptors (e.g., carvedilol).

EFFECT OF BETA-BLOCKERS IN THE MANAGEMENT OF HF. Beta-blockers have now been evaluated in more than 10,000 patients with HF who participated in more than 20 published placebo-controlled clinical trials (173-176). All trials enrolled patients with systolic dysfunction (ejection fraction less than 0.35 to 0.45) who had already been treated with diuretics and an ACE inhibitor, 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 left ventricular 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. A recently completed prospective trial with carvedilol that enrolled clinically stable patients with severe symptoms demonstrated a reduction in mortality in patients with such advanced disease (177).

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 overall sense of well-being (178-185). In addition, like ACE inhibitors, beta-blockers can reduce the risk of death and the combined risk of death or hospitalization (174-177;186). These benefits of beta-blockers were seen in patients with or

without coronary artery disease and in patients with or without diabetes. The favorable effects of beta-blockers were also observed in patients already taking ACE inhibitors, which suggests that combined blockade of 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 left ventricular systolic dysfunction unless they have a contraindication to their use or have been shown to be unable to tolerate treatment with these drugs.

Because of its favorable effects on survival, treatment with a beta-blocker should not be delayed until the patient is found to be resistant to treatment with other drugs. Although it is commonly believed (incorrectly) that patients who have mild symptoms or who appear clinically stable do not require additional treatment, such patients are at high risk for morbidity and mortality and are likely to deteriorate during the ensuing 12 months even if treated with digitalis, diuretics, and ACE inhibitors (185). Therefore, even if they do not benefit symptomatically because they have little disability, patients with mild symptoms should receive treatment with a beta-blocker to reduce the risk of disease progression, future clinical deterioration, and sudden death (174-176;185;186).

In general, beta-blockers are used together with an ACE inhibitor (and usually with digitalis). Patients need not be taking high doses of ACE inhibitors before being considered for treatment with a beta-blocker, because most patients enrolled in the beta-blocker trials were not taking high doses of ACE inhibitors. Furthermore, in patients taking a low dose of an ACE inhibitor, 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 ACE inhibitor, even to the target doses used in clinical trials (147;187). Beta-blockers 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 fluid retention that can accompany the initiation of beta-blocker therapy (188-190).

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. Patients should not take a beta-blocker if they have reactive airways disease or if they have symptomatic bradycardia or advanced heart block (unless treated with a pacemaker).

Initiation and maintenance. Treatment with a beta-blocker should be initiated at very low doses, 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 (188-190), 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 (174-177).

What dose of a beta-blocker should physicians try to achieve in patients with HF? As with ACE inhibitors, 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 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 be maintained on 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 (106). 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 (191).

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

1. Fluid retention and worsening HF. Initiation of therapy with a beta-blocker can cause fluid retention (188-190),

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 (192). 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.

2. 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.

3. 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. In selected patients, the benefits of beta-blockers may be sufficiently important that, if low doses of these drugs caused symptomatic bradycardia or heart block, it would be reasonable to consider cardiac pacing to allow the use of beta-blockers.

4. 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 (174). For beta blockers that also block alpha-receptors, such as carvedilol, these vasodilatory side effects are generally seen within 24 to 48 h 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 ACE inhibitor at different times during the day. If this is ineffective, the occurrence of hypotension may require a temporary reduction in the dose of the ACE inhibitor. 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 (188-190).

d. 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) (193). 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 (194;195). In addition, by inhibiting $\text{Na}^+\text{-K}^+$ ATPase in the kidney, digitalis reduces the renal tubular reabsorption of sodium (196); the resulting increase in the delivery of sodium to the distal tubules leads to the suppression of renin secretion from the kidneys (197). 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 (198). 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 (103;199-204). These benefits have been seen regardless of the underlying rhythm (normal sinus rhythm or atrial fibrillation), cause of HF (ischemic or nonischemic cardiomyopathy), or concomitant therapy (with or without ACE inhibitors). 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 little effect on mortality but modestly reduced the combined risk of death and hospitalization (64).

PRACTICAL USE OF DIGITALIS IN HF. *Selection of patients.* Physicians should consider using digoxin to improve the symptoms and clinical status of patients with HF, in conjunction with diuretics, an ACE inhibitor, and a beta-blocker. Digoxin may be used early to reduce symptoms in patients who have been started on, but have not yet responded symptomatically to, treatment with an ACE inhibitor or a beta-blocker. Alternatively, treatment with digoxin may be delayed until the patient's response to ACE inhibitors and beta-blockers has been defined and used only in patients who remain symptomatic despite therapy with the neurohormonal antagonists. If a patient is taking digoxin but not an ACE inhibitor or a beta-blocker, treatment with digoxin should not be withdrawn, but appropriate therapy with the neurohormonal antagonists should be instituted. Digoxin is prescribed routinely in patients with HF who have chronic atrial fibrillation, but beta-blockers may be more effective in controlling the ventricular response, especially during exercise (205-207).

Digoxin is not indicated as primary therapy for the stabilization of patients with acutely decompensated HF. Such patients should first receive appropriate treatment for HF (usually with intravenous medications); therapy with digoxin may be initiated at the same time 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 treated with a permanent pacemaker. The drug should be used cautiously in patients taking other drugs that can depress sinus or atrioventricular nodal function (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 used, digoxin is the most commonly used formulation in the United States 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 if the patient is over 70 years old, has impaired renal function, or has a low lean body mass (208). 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.

Although some physicians have advocated using serum levels to guide the selection of the dose of digoxin (209), there is little evidence to support such an approach. The radioimmunoassay for digoxin was developed to assist in the evaluation of the toxicity and not the efficacy of the drug (210;211). When used for the treatment of HF, there may be little relationship between serum digoxin concentration and the drug's therapeutic effects, and data suggest that large doses of digoxin may not be more effective than small doses in the treatment of HF (212-214).

Risks of treatment. Although physicians have traditionally been taught that digitalis produces frequent side effects, the drug (as currently prescribed) is well tolerated by most patients with HF (215). The principal adverse reactions occur primarily when digoxin is administered in large doses, but large doses may not be needed to produce clinical benefits (212-214). 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). Digitalis toxicity is commonly associated with serum digoxin levels more than 2 ng per mL but may occur with lower digoxin levels, especially if hypokalemia, hypomagnesemia, or hypothyroidism co-exist (216;217). The concomitant use of quinidine, verapamil, spironolactone, flecainide, propafenone, or amiodarone can increase serum digoxin levels and may increase the likelihood of digitalis toxicity (218-224). The dose of

digoxin should be reduced if treatment with these drugs is initiated. 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.

In addition to these established side effects, there is concern that levels of digoxin that are generally considered to be in the therapeutic range (0.7 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 myocardial infarction (64). 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 (225).

3. Interventions to be Considered for Use in Selected Patients

Controlled clinical trials have shown some interventions to be useful in a limited cohort of patients with HF. Several of these agents are undergoing active investigation in large-scale trials to determine whether their role in the management of HF might be justifiably expanded.

a. Aldosterone Antagonists

Although short-term therapy with both ACE inhibitors and angiotensin II receptor antagonists can lower circulating levels of aldosterone, it is not clear that such suppression is sustained during long-term treatment (226). The lack of long-term suppression may be important, because experimental data suggest that aldosterone may exert adverse effects on the structure and function of the heart, independently of and in addition to the deleterious effects produced by angiotensin II (227-233).

Spironolactone is the only aldosterone antagonist available for clinical use in the United States. In a large-scale, long-term trial (85), the addition of low doses of spironolactone to therapy for patients with recent or current class IV symptoms who were taking an ACE inhibitor reduced the risk of death and hospitalization. The most marked effects were seen in patients who were also given digitalis and beta-blockers. The most important adverse reactions of spironolactone in clinical trials were hyperkalemia and gynecomastia (in men) (85;234).

RECOMMENDATIONS CONCERNING ALDOSTERONE ANTAGONISTS. The addition of low doses of spironolactone should be considered in patients with recent or current symptoms at rest despite the use of digoxin, diuretics, an ACE inhibitor, and (usually) a beta-blocker. Patients should have a serum potassium level less than 5.0 mmol per L and a serum creati-

nine level less than 2.5 mg per dL before therapy is initiated, and both variables should be monitored closely during treatment. Hyperkalemia may complicate treatment at any time and lead to life-threatening cardiac bradyarrhythmias. It is therefore prudent to reduce or stop potassium supplements when therapy with spironolactone is started. If the serum potassium increases to a level more than 5.4 mmol per L, physicians should reduce the dose of spironolactone. The drug should be stopped if serious hyperkalemia develops or the patient develops painful gynecomastia. The role of spironolactone in patients with mild to moderate HF has not been defined, and use of the drug cannot be recommended in such individuals.

b. Angiotensin Receptor Blockers

An alternative approach to inhibiting the actions of angiotensin II in patients with HF is the use of drugs that block the angiotensin II receptor. These agents were developed on the premise that interference with the renin-angiotensin system without inhibition of kininase would produce all of the benefits of ACE inhibitors while minimizing the risk of their adverse reactions (235). This premise was based on the belief that the benefits of ACE inhibitors were related to the suppression of angiotensin II formation, whereas the side effects of ACE inhibitors were related to the accumulation of kinins. However, it is now known that many of the side effects of ACE inhibitors in HF are related to the suppression of angiotensin II formation (236), whereas some of the benefits may be related to the accumulation of kinins (125-127).

Several angiotensin II receptor antagonists (e.g., candesartan, eprosartan, irbesartan, losartan, telmisartan, and valsartan) are available for clinical use. Experience with these drugs in controlled clinical trials of patients with HF is considerably less than that with ACE inhibitors. Nevertheless, in several placebo-controlled studies, long-term therapy with angiotensin receptor antagonists produced hemodynamic, neurohormonal, and clinical effects consistent with those expected after interference with the renin-angiotensin system (237-243). Although an early pilot study raised the possibility that an angiotensin receptor blocker might have mortality effects superior to those of an ACE inhibitor (244), this was not confirmed in a second trial (242) or in a large definitive study (146). Both trials showed a trend for a better survival in patients treated with an ACE inhibitor than in those treated with an angiotensin receptor blocker.

The use of angiotensin II receptor antagonists as an adjunct to other therapy for HF (including ACE inhibitors) was the subject of a large trial [J.N. Cohn, oral presentation of the results of the Valsartan in Heart Failure (Val-HeFT) Trial, AHA Annual Scientific Sessions, Atlanta, Ga, November, 2000]. In a preliminary report, valsartan (target dose 160 mg twice daily) reduced the endpoint of combined mortality and morbidity (including sudden death, hospitalization, and administration of intravenous inotropic or vasodilating agents for HF). All-cause mortality (a co-primary endpoint)

was not improved by valsartan. Subgroup analysis, which should be interpreted with considerable caution, suggested that patients who were already taking both a beta-blocker and an ACE inhibitor did not benefit from the addition of valsartan with respect to the combined endpoint. Peer review and final publication of these data will be necessary to clarify this issue.

RECOMMENDATIONS CONCERNING ANGIOTENSIN RECEPTOR BLOCKERS. Angiotensin receptor blockers should not be considered equivalent or superior to ACE inhibitors in the treatment of HF, and thus, they should not be used for the treatment of HF in patients who have no prior use of an ACE inhibitor and should not be substituted for ACE inhibitors in patients who are tolerating ACE inhibitors without difficulty. Angiotensin receptor blockers should be considered instead of ACE inhibitors primarily in patients who are intolerant of ACE inhibitors because of angioedema or intractable cough. Angiotensin receptor blockers are as likely as ACE inhibitors to produce hypotension, worsening renal function, and hyperkalemia.

The role of angiotensin receptor blockers as an adjunct to ACE inhibitors remains to be defined. Until further data are available, beta-blockers, rather than angiotensin receptor antagonists, should be added to patients with HF who are taking an ACE inhibitor, and angiotensin receptor antagonists should not be given to patients taking an ACE inhibitor and a beta-blocker.

c. Hydralazine and Isosorbide Dinitrate

Although isosorbide dinitrate and hydralazine were initially combined because of their complementary dilating actions on peripheral blood vessels (245;246), recent evidence suggests that hydralazine and isosorbide dinitrate may also act at a biochemical and genetic level. Nitrates can inhibit abnormal myocardial and vascular growth (247;248) and may thereby attenuate the process of ventricular remodeling (249). Theoretically, hydralazine may interfere with the biochemical and molecular mechanisms responsible for the progression of HF (250;251), as well as the development of nitrate tolerance (252-255).

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 ACE inhibitor or beta-blocker (256;257). However, in another large-scale trial that compared the vasodilator combination with an ACE inhibitor, the ACE inhibitor produced more favorable effects on survival (144). 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.

There is no controlled experience with the addition of hydralazine and isosorbide dinitrate to therapy with an ACE inhibitor or a beta-blocker. Similarly, there are no specific

data on the effects of the vasodilator combination in patients with HF who are unable to tolerate treatment with ACE inhibitors or beta-blockers.

RECOMMENDATIONS CONCERNING HYDRALAZINE AND ISOSORBIDE DINITRATE. 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 ACE inhibitor and should not be substituted for ACE inhibitors in patients who are tolerating ACE inhibitors without difficulty.

Despite the lack of data with the vasodilator combination in patients who are intolerant of ACE inhibitors, the combined use of hydralazine and isosorbide dinitrate may be considered as a therapeutic option in such patients, particularly in those who cannot take an ACE inhibitor because of hypotension or renal insufficiency. However, compliance with this combination has generally been poor because of the large number of tablets required and the high incidence of adverse reactions (144;256). Therefore, many physicians prefer the use of angiotensin II antagonists in patients who cannot tolerate an ACE inhibitor because of cough or angioedema.

There are no controlled trials evaluating the utility of the hydralazine and isosorbide dinitrate combination in patients already being given an ACE inhibitor. In such patients, other agents (e.g., beta-blockers) should be considered first. There are also no large-scale trials that support the use of nitrates alone or hydralazine alone in the treatment of HF.

d. Exercise Training

In the past, patients with HF were advised to avoid physical exertion in the hope that bed rest might minimize symptoms (258) and in the belief that physical activity might accelerate the progression of left ventricular dysfunction (259-261). 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 (70;73). Limitations of activity may not only impair exercise capacity but may also produce adverse psychological effects and impair peripheral vasodilatory responses (72;262). These findings have led to the hypothesis that exercise training might improve the clinical status of patients with chronic HF (70;263).

Several controlled trials have shown that exercise training can lessen symptoms, increase exercise capacity and improve the quality of life of patients with chronic HF (264-274). The improvement was comparable to that achieved with pharmacological interventions (263), was additive to the benefits of ACE inhibitors and beta-blockers (266;267), and was associated with an enhancement of endothelium-dependent peripheral vasodilation and skeletal muscle metabolism (266;275). In these studies, physical conditioning was generally accomplished in the context of a formal program, which required patients to gradually achieve workloads of 40% to 70% of maximal effort for 20 to 45 min 3 to 5 times a week for periods of 8 to 12 weeks (273).

The long-term effects of exercise training have not been completely defined. In short-term studies, exercise training has been accompanied by a reduction in the activation of neurohormonal systems and attenuation of the process of ventricular remodeling (264;268;276). In the experimental setting, exercise appears to attenuate the rate of progression of HF (277;278). These observations suggest that exercise training might have a favorable effect on the natural history of HF. Only one study has evaluated the long-term effect of physical conditioning in patients with HF (274), and in this trial, exercise training was associated with a reduction in the risk of hospitalization and death. Little work has been conducted to identify patients most likely to respond favorably to training and to define optimal exercise protocols.

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.

4. Drugs and Interventions Under Active Investigation

Several drugs and interventions are under active evaluation in long-term large-scale trials because they showed promise in pilot studies that involved small numbers of patients. Until the results of definitive trials are available, none of these interventions can be recommended for use in patients with HF.

a. Vasopeptidase Inhibitors

The syndrome of HF is characterized not only by enhanced activation of endogenous vasoconstrictor neurohormonal systems (e.g., renin-angiotensin system), but also by the diminished responses to endogenous vasodilator systems (e.g., natriuretic peptides (279-282)). Hence, there has been interest in the development of vasopeptidase inhibitors that block not only the ACE, which leads to decreased levels of angiotensin II, but also the neutral endopeptidase, which leads to enhanced activity of endogenous vasodilators (283). One vasopeptidase inhibitor, omapatrilat, is being developed for the treatment of hypertension and for the treatment of HF. In experimental and small-scale clinical studies, omapatrilat produced an improvement in cardiac performance and a reduction in the risk of death and worsening HF to a greater degree than a conventional ACE inhibitor (284-287). The possibility that omapatrilat may be superior to an ACE inhibitor is now being evaluated in a large-scale trial.

b. Cytokine Antagonists

Patients with HF have elevated levels of the cytokine, tumor necrosis factor (288;289), which can exert cardiodepressant and cardiotoxic effects in experimental models (290;291). The major source of tumor necrosis factor may be the heart itself, which appears to synthesize the cytokine in response

to hemodynamic stresses (292;293). Two types of tumor necrosis factor antagonists are commercially available: a soluble receptor (etanercept) and a chimeric antibody (infliximab). Both are available for use in the management of non-cardiovascular disorders (294-296) and are undergoing evaluation for use in the treatment of HF. In a short-term pilot study, etanercept produced dose-dependent increases in ejection fraction, decreases in left ventricular chamber size, and improvement in clinical status (297;298). However, a large-scale trial with etanercept in HF was stopped early because of the low likelihood that the drug would show favorable effects. Alternative approaches to cytokine inhibition are being evaluated at the present time, but until definitive studies with these newer agents are completed, cytokine antagonists cannot be recommended for the treatment of HF.

c. Endothelin Antagonists

Endothelin is a potent vasoconstrictor that can adversely affect the structure and function of the heart and peripheral blood vessels (299-301). Circulating levels of endothelin-1 are elevated in patients with HF, and endothelin antagonism can produce favorable hemodynamic and prognostic effects in experimental models of HF (301-303). Two types of endothelin-1 antagonists are under evaluation: those that block the receptors for endothelin-1, and those that inhibit the endothelin converting-enzyme, which is responsible for the formation of endothelin-1. In two small pilot studies, high doses of the endothelin receptor antagonist bosentan produced favorable effects on cardiac performance and clinical status (304;305) but were associated with liver-function abnormalities. In another recently completed trial, treatment with the endothelin antagonist enrasentan was associated with no improvement in symptoms and an increased risk of worsening HF (W.T. Abraham, oral presentation, ACC Annual Scientific Sessions, Orlando, Fla, March, 2001). The utility of low doses of bosentan is now being evaluated in a large-scale trial. No endothelin antagonist is presently available for clinical use for any indication.

d. Synchronized Biventricular Pacing

Many patients with HF have asynchronous ventricular electrical activation (as reflected by a prolonged QRS duration on the surface electrocardiogram), which may contribute to the hemodynamic abnormalities and poor prognosis of the syndrome (306;307). Such asynchronous contraction can be addressed by electrically activating the right and left ventricles in a synchronized manner with a pacemaker; this may enhance ventricular contraction and reduce the degree of secondary mitral regurgitation that results from delayed septal activation (308-310). In controlled and uncontrolled trials of up to 6 months' duration, patients treated with cardiac resynchronization showed greater improvement in symptoms and exercise tolerance than patients in the control group (W.T. Abraham, oral presentation on the Multicenter Insync RAndomized CLinical Evaluation (MIRACLE) Trial, ACC

Annual Scientific Session, Orlando, Florida, March 2001) (311;313). The long-term effects of cardiac resynchronization are unknown but are being evaluated in several studies.

e. External Counterpulsation

External counterpulsation involves the use of an inflatable suit that surrounds the lower limbs and expands to compress the extremities during diastole. Use of this device is intended to mimic the effects of intra-aortic balloon counterpulsation, which reduces loading conditions in systole while increasing coronary perfusion pressures in diastole. External counterpulsation has been shown to reduce the frequency and severity of anginal attacks in patients with symptomatic coronary artery disease (314), and is undergoing evaluation in clinical trials for chronic HF. Until more data are available, this approach cannot be recommended for the management of patients with symptomatic left ventricular systolic dysfunction.

f. Techniques for Respiratory Support

Patients with HF frequently exhibit abnormal respiratory patterns, including Cheynes-Stokes breathing and sleep apnea (315). The use of nocturnal oxygen and devices that provide continuous positive airway pressure has been reported to ameliorate these respiratory abnormalities and produce symptomatic improvement (316-318). Additional studies are in progress to evaluate the efficacy of these interventions. It is hoped that such studies will provide information about the efficacy and safety of this approach and help to identify patients most likely to benefit from treatment.

5. Drugs and Interventions of Unproved Value and Not Recommended

a. Nutritional Supplements and Hormonal Therapies

Several nutritional supplements (e.g., coenzyme Q10, carnitine, taurine, and antioxidants) or hormonal therapies (e.g., growth hormone or thyroid hormone) have been proposed for the treatment of HF (319-324). However, several controlled trials have shown that these nutritional approaches are not different from placebo in their effects on the survival or clinical status of patients (325-329). Furthermore, the mechanisms by which these agents are supposed to have beneficial effects have not been validated, and any claim that these supplements represent a "natural" approach must be considered speculative. Importantly, the short- and long-term safety of these supplements has not been evaluated, and there are concerns that use of certain agents may have deleterious effects on the heart or interact adversely with drugs known to be of value in patients with HF (328;330;331). Therefore, until more data are available, nutritional supplements or hormonal therapies are not recommended for the treatment of HF. Because patients can initiate such treatments without a prescription, physicians caring for patients with HF should rou-

tinely inquire about their use and explain the lack of evidence supporting their use.

b. Intermittent Intravenous Positive Inotropic Therapy

Although positive inotropic agents can improve cardiac performance during short- and long-term therapy (332;333), long-term oral therapy with these drugs has not improved symptoms or clinical status (202;334-344) and has been associated with a significant increase in mortality, especially in patients with advanced HF (342;345-350). Despite these data, some physicians have proposed that the regularly scheduled intermittent use of intravenous positive inotropic drugs (e.g., dobutamine or milrinone) in a supervised outpatient setting might be associated with some clinical benefits (23-25;351).

However, there has been little experience with intermittent home infusions of positive inotropic agents in controlled clinical trials. Nearly all of the available data are derived from open-label and uncontrolled studies or from trials that have compared one inotropic agent with another, without a placebo group (23-25;351). Most trials have been small and short in duration and thus have not been able to provide reliable information about the effect of treatment on the risk of serious cardiac events. Much if not all of the benefit seen in these uncontrolled reports may have been related to the increased surveillance of the patient's status and intensification of concomitant therapy, and not to the use of positive inotropic agents. Only one placebo-controlled trial of intermittent intravenous positive inotropic therapy has been published (352), and its findings are consistent with the results of long-term studies with continuous oral positive inotropic therapy in HF (e.g., with milrinone), which showed little efficacy and were terminated early because of an increased risk of death.

Because of lack of evidence to support their efficacy and concerns about their toxicity, physicians should not utilize *intermittent* infusions of positive inotropic agents (at home, in an outpatient clinic, or in a short-stay unit) in the long-term treatment of HF, even in its advanced stages. The use of continuous infusions of positive inotropic agents as palliative therapy in patients with end-stage disease (stage D) is discussed later in this document.

c. Dynamic Cardiomyoplasty

This technique involves prolonged pacing of the latissimus dorsi to convert its structural and functional properties to those of cardiac muscle, followed by wrapping of the skeletal muscle around the heart (353;354). Advocates of the procedure have suggested that it might produce beneficial effects by enhancing systolic contraction or by limiting ventricular dilatation (355;356). In uncontrolled studies, the use of dynamic cardiomyoplasty was associated with symptomatic improvement in some patients (353;354), but subsequent experience has not confirmed the benefits of this procedure (357;358). Dynamic cardiomyoplasty is not recommended for the treatment of HF.

Recommendations for Treatment of Symptomatic Left Ventricular Systolic Dysfunction (Stage C)

Class I

1. **Diuretics in patients who have evidence of fluid retention.** (*Level of Evidence: A*)
2. **ACE inhibition in all patients, unless contraindicated (see text).** (*Level of Evidence: A*)
3. **Beta-adrenergic blockade in all stable patients, unless contraindicated [see text]. Patients should have no or minimal evidence of fluid retention and should not have required treatment recently with an intravenous positive inotropic agent.** (*Level of Evidence: A*)
4. **Digitalis for the treatment of symptoms of HF, unless contraindicated [see text].** (*Level of Evidence: A*)
5. **Withdrawal of drugs known to adversely affect the clinical status of patients (e.g., nonsteroidal anti-inflammatory drugs, most antiarrhythmic drugs, and most calcium channel blocking drugs; see text).** (*Level of Evidence: B*)
6. **Measures listed as Class I recommendations for patients in stages A and B.** (*Levels of Evidence: A, B, and C as appropriate*).

Class IIa

1. **Spirolactone in patients with recent or current Class IV symptoms, preserved renal function and a normal potassium concentration.** (*Level of Evidence: B*)
2. **Exercise training as an adjunctive approach to improve clinical status in ambulatory patients.** (*Level of Evidence: A*)
3. **Angiotensin receptor blockade in patients who are being treated with digitalis, diuretics, and a beta-blocker and who cannot be given an ACE inhibitor because of cough or angioedema.** (*Level of Evidence: A*)
4. **A combination of hydralazine and a nitrate in patients who are being treated with digitalis, diuretics, and a beta-blocker and who cannot be given an ACE inhibitor because of hypotension or renal insufficiency.** (*Level of Evidence: B*)

Class IIb

1. **Addition of an angiotensin receptor blocker to an ACE inhibitor.** (*Level of Evidence: B*)
2. **Addition of a nitrate (alone or in combination with hydralazine) to an ACE inhibitor in patients who are also being given digitalis, diuretics, and a beta-blocker.** (*Level of Evidence: B*)

Class III

1. **Long-term intermittent use of an infusion of a positive inotropic drug.** (*Level of Evidence: C*)
2. **Use of an angiotensin receptor blocker instead of an ACE inhibitor in patients with HF who have not been given or who can tolerate an ACE inhibitor.** (*Level of Evidence: B*)

3. **Use of an angiotensin receptor blocker before a beta-blocker in patients with HF who are taking an ACE inhibitor. (Level of Evidence: A)**
4. **Use of a calcium channel blocking drug as a treatment for HF. (Level of Evidence: B)**
5. **Routine use of nutritional supplements (coenzyme Q10, carnitine, taurine, and antioxidants) or hormonal therapies (growth hormone or thyroid hormone) for the treatment of HF. (Level of Evidence: C)**

D. Patients With Refractory End-Stage HF

Most patients with HF due to left ventricular systolic dysfunction 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 (also see Section V).

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 (92;108). 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) (115;117). If the patient continues to exhibit evidence of volume overload despite these measures, hospitalization is generally required to allow patients to receive high doses of diuretics intravenously (114), either alone or in conjunction with drugs that can increase renal blood flow (e.g., intravenous dopamine and dobutamine) (359). 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 ACE inhibitor. Provided 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 (360;361). 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 (362), because unresolved edema may itself attenuate the response to diuretics (110-112). 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. 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 (87-90).

2. Utilization of Neurohormonal Inhibitors

Controlled trials suggest that patients with advanced HF respond favorably to treatment with both ACE inhibitors and beta-blockers in a manner similar to those with mild to moderate disease (145;177). 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 ACE inhibitor 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.

Consequently, physicians should exercise great care when considering the use of both ACE inhibitors 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 ACE

inhibitor 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 (187;363).

Patients who cannot tolerate ACE inhibitors or beta-blockers may be considered for alternative pharmacological treatments. 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 ACE inhibitor or a beta-blocker (256), 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 that 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 (85). 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 angiotensin II antagonists (235) are frequently considered as alternatives to ACE inhibitors because of their low incidence of cough and angioedema, it is not clear that angiotensin II antagonists are as effective as ACE inhibitors, and they are as likely as ACE inhibitors to produce hypotension or renal insufficiency (146;244).

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 or nitroprusside) 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 (364). 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 (191;365). 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 h after the infusions are discontinued (366).

Patients who cannot be weaned from intravenous to oral therapy on multiple occasions may require placement of an indwelling line to allow for the continuous infusion of dobutamine or milrinone. 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 are not being considered for transplantation but 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 inotropic support can provide palliation of symptoms as part of an overall plan to allow the patient to die with comfort at home (367;368). The use of continuous intravenous inotropic support to allow hospital discharge should be distinguished from the intermittent administration of infusions of positive inotropic agents to patients who have been successfully weaned from inotropic support. The long-term use of regularly scheduled intermittent infusions at home, in an outpatient clinic, or in a short-stay unit is strongly discouraged, even in advanced HF (23-25;352).

4. Mechanical and Surgical Strategies

Cardiac transplantation is currently the only established surgical approach to the treatment of refractory HF, but it is available to fewer than 2500 patients in the United States each year (369;370). Current indications for cardiac transplantation have been developed by broad consensus and focus on the identification of patients with severe functional impairment, as indicated by a peak exercise oxygen consumption of less than 15 mL per kg per min (or less than 50% of predicted normal) or continued dependence on intravenous inotropic agents (Table 3). Less common indications for cardiac transplantation include recurrent life-threatening ventricular arrhythmias or angina that is refractory to all currently available treatments.

Alternate surgical and mechanical approaches for the treatment of end-stage HF are under development. Hemodynamic and clinical improvement has been reported after mitral valve repair or replacement in patients who have clinically important degrees of mitral regurgitation that is secondary to left ventricular dilatation (67). However, no controlled studies have evaluated the effects of this procedure on ventricular function, clinical status, or survival. Extra-corporeal devices are approved for circulatory support in patients who are expected to recover from a major cardiac insult (e.g., myocardial ischemia, post-cardiotomy shock, or fulminant myocarditis) or are expected to undergo a definitive treatment for HF (e.g., heart transplantation). Left ventricular assist devices provide similar degrees of hemodynamic support but many are implantable and thus allow for patient ambulation and hospital discharge (371). An ongoing trial is evaluating the long-term utility of such a device in patients with refractory HF who are not candidates for a heart trans-

Table 3. Indications for Cardiac Transplantation

Absolute indications

- For hemodynamic compromise due to HF
 - Refractory cardiogenic shock
 - Documented dependence on IV inotropic support to maintain adequate organ perfusion
 - Peak VO₂ less than 10 mL per kg per min with achievement of anaerobic metabolism
- Severe symptoms of ischemia that consistently limit routine activity and are not amenable to coronary artery bypass surgery or percutaneous coronary intervention
- Recurrent symptomatic ventricular arrhythmias refractory to all therapeutic modalities

Relative Indications

- Peak VO₂ 11 to 14 mL per kg per min (or 55% predicted) and major limitation of the patient's daily activities
- Recurrent unstable ischemia not amenable to other intervention
- Recurrent instability of fluid balance/renal function not due to patient noncompliance with medical regimen

Insufficient Indications

- Low left ventricular ejection fraction
- History of functional class III or IV symptoms of HF
- Peak VO₂ greater than 15 mL per kg per min (and greater than 55% predicted) without other indications

HF indicates heart failure.

plant (372). Some reports have suggested that prolonged mechanical decompression of the failing heart (i.e., for many months) may result in sufficient recovery of myocardial function to allow explantation of the device (373), but this appears to be an infrequent phenomenon (374). Finally, although both left ventriculectomy (Batista procedure) and cardiomyoplasty have generated considerable excitement as potential surgical approaches to the treatment of end-stage HF (353;375), these procedures failed to result in clinical improvement and were associated with a high risk of death (376). A variant of the aneurysmectomy procedure is now being developed for the management of patients with ischemic cardiomyopathy (377), but its role in the management of HF remains to be defined.

Recommendations for Patients With Refractory End-Stage HF (Stage D)

Class I

1. Meticulous identification and control of fluid retention. (*Level of Evidence: B*)
2. Referral for cardiac transplantation in eligible patients. (*Level of Evidence: B*)
3. Referral to an HF program with expertise in the management of refractory HF. (*Level of Evidence: A*)
4. Measures listed as class I recommendations for patients in Stages A, B, and C. (*Levels of Evidence: A, B, and C as appropriate*).

Class IIb

1. Pulmonary artery catheter placement to guide therapy in patients with persistently severe symptoms. (*Level of Evidence: C*)
2. Mitral valve repair or replacement for severe secondary mitral regurgitation. (*Level of Evidence: C*)

3. Continuous intravenous infusion of a positive inotropic agent for palliation of symptoms. (*Level of Evidence: C*)

Class III

1. Partial left ventriculectomy. (*Level of Evidence: C*)
2. Routine intermittent infusions of positive inotropic agents. (*Level of Evidence: B*)

V. TREATMENT OF SPECIAL POPULATIONS AND CONCOMITANT DISORDERS

Many patients with HF are members of subpopulations who are likely to exhibit unique responses or who have comorbid conditions that accelerate the development or progression of HF or complicate the management of HF.

A. Special Populations

1. Women and Men

Many physicians regard HF primarily as a disease of men, because coronary risk factors are common in men and because primarily men are enrolled in clinical trials of treatments for HF. However, the majority of patients with HF in the general population are women (particularly elderly women) who frequently have HF associated with diastolic dysfunction. Even HF due to systolic dysfunction may be different in women than in men. Yet, most large, multicenter trials have not included sufficient numbers of women to allow conclusions about the efficacy and safety of their treatment. Several studies have documented a lower use of ACE-inhibitors in women with HF than in men (378), and another study reported that women are given fewer cardiovascular medications after a myocardial infarction than men (379-381). These findings may explain why women have been

noted to rate their quality of inpatient care lower than men and why they have less improvement in physical health status after an episode of HF (380). One report (but not others) suggested that women with HF do not show survival benefits from ACE inhibition (382). Women may also have a different safety profile than men, as evidenced by their higher risk of ACE inhibitor-induced cough (383). Currently, great efforts are being made (and mandated) to include a higher proportion of women in government sponsored trials.

Because HF is frequently accompanied by erectile dysfunction, men may express interest in the use of sildenafil as a means of enhancing sexual performance. Few patients with HF were enrolled in controlled trials with sildenafil, and thus, the efficacy and safety of this drug in patients with left ventricular dysfunction are not known. Nevertheless, recent studies suggest that sildenafil may produce hemodynamic benefits in patients with coronary artery disease and may act to improve some of the peripheral vascular abnormalities that characterize patients with HF (384). Although patients with HF appear to tolerate short-term administration of the drug without difficulty, sildenafil should not be given to patients taking nitrates, who may experience profound hypotension due to its ability to potentiate the systemic vasodilator effects of drugs that increase intracellular levels of cyclic AMP (385).

2. Racial Minorities

Heart failure is a major public health problem in blacks. Heart failure is more common in the black population, affecting approximately 3% of all adult black Americans. Black patients develop symptoms of HF at an earlier age than non-black patients, possibly because black patients are more likely to have hypertension and diabetes than nonblack patients and because they more frequently exhibit sodium retention, ventricular hypertrophy, and vascular injury. Once the diagnosis is made, HF progresses more rapidly in black than in white patients, as evidenced by a higher risk of initial and recurrent hospitalization and death (386-388). This risk cannot be explained by the presence of coronary artery disease, which is less common in black than in non-black patients with HF.

Because racial minorities with HF are under-represented in clinical trials of new drugs for HF, little is known about their response to medications used in the management of this disease. Clinical experience suggests that Asian patients have an extraordinarily high risk of cough (nearly 50%) during treatment with an ACE inhibitor. Retrospective analysis of subgroup data has suggested that—as in the treatment of hypertension—black patients with HF may derive less benefit than nonblack patients from the use of ACE inhibitors (389). A recent analysis of a large HF trial, that used a matched-cohort design, confirmed that black patients had higher rates from death of any cause and a greater number of hospitalizations for HF than matched white patients (390). Interestingly, the results of 2 trials evaluating the effects of different beta-blockers in black patients have been discordant: bucindolol

caused a nonsignificant increase in the risk of a serious clinical event in black patients, but it reduced death or hospitalization in non-black patients (391). Conversely, the benefit of carvedilol in a separate series of trials was apparent and of a similar magnitude in both black and non-black patients with HF (392). There may be race-based differences in the outcome of cardiac transplantation as well (393). Further study is needed to clarify these issues.

3. Elderly Patients

Heart failure is particularly common in elderly patients. Approximately 6% to 10% of the population 65 years or older have HF (394), and HF is the most common reason for hospitalization in elderly patients (395-398). The high prevalence of HF in old people may be related to age-related changes in ventricular function (particularly diastolic function) (399-403). In addition, risk factors for HF (e.g., hypertension, diabetes, hyperlipidemia) are generally not treated aggressively in the elderly, yet elderly patients commonly take medications that can exacerbate the syndrome of HF (e.g., nonsteroidal anti-inflammatory drugs) (76).

Heart failure in elderly patients is inadequately recognized and treated (404). Both patients and physicians frequently attribute the symptoms of HF to aging, and noninvasive cardiac imaging commonly fails to reveal impaired systolic function, because diastolic dysfunction is a major cause of HF in old people. In addition, some reports suggest that elderly patients may have diminished responses to diuretics, ACE inhibitors, and positive inotropic agents (405-407) compared with younger patients and may experience a higher risk of adverse effects attributable to treatment (381;408-412). Uncertainties regarding the relation of risk-to-benefit are exacerbated by the fact that very old individuals are poorly represented in large-scale clinical trials designed to evaluate the efficacy and safety of new treatments for HF.

Some multidisciplinary HF programs have been successful in decreasing the rate of readmission and associated morbidity in elderly patients (87;413). Managed care organizations continue to struggle with improved ways of implementing these pathways (414;415).

B. Patients With HF Who Have Concomitant Disorders

Patients with severe left ventricular systolic dysfunction frequently have associated cardiovascular and noncardiovascular disorders, whose course or treatment may exacerbate the syndrome of HF. In many patients, appropriate management of these concomitant illnesses may produce symptomatic and prognostic benefits that may be as important as the treatment of the HF condition itself.

1. Cardiovascular Disorders

a. Hypertension, Hyperlipidemia, and Diabetes Mellitus

Approximately two thirds of patients with HF have a past or current history of hypertension, and approximately one third

have diabetes mellitus (416). Both disorders can contribute to the development of systolic or diastolic dysfunction (417;418), either directly or by contributing (together with hyperlipidemia) to the development of coronary artery disease (419;420). Long-term treatment of both hypertension and hyperlipidemia can decrease the risk of developing HF (33;34;45;421;422). In a large-scale trial, the administration of a lipid-lowering agent to patients with hypercholesterolemia and a history of myocardial infarction reduced all-cause mortality and the risk of developing HF (45;421). In 2 large-scale multicenter studies, the treatment of hypertension reduced both the risk of death and the risk of HF; this was true regardless of whether the elevation of blood pressure was primarily systolic or diastolic (33;34;422). The benefits of lowering blood pressure may be particularly marked in patients with diabetes mellitus (37;41;423).

Interestingly, the presence of or treatment for HF may complicate the management of both hypertension and diabetes. Many antihypertensive agents should be avoided in patients with HF because of their ability to depress cardiac function or to lead to salt and water retention. In addition, HF itself is associated with resistance to the actions of insulin (424;425), and the resulting hyperinsulinemia may promote both cardiac and vascular hypertrophy (426-428) and thus may hasten the progression of HF. These mechanisms may help to explain why diabetic patients with HF have a worse prognosis than their nondiabetic counterparts (40). Clinical experience has shown that one side effect of newer oral agents of the thiazolidinedione class is weight gain, which is due in part to fluid retention. This effect may have the potential to precipitate or exacerbate HF in patients with reduced cardiac reserve. Thiazolidinediones probably should be used with caution in such patients (429).

RECOMMENDATIONS CONCERNING MANAGEMENT. Little is known about the benefits of treating hypertension, hypercholesterolemia, or diabetes mellitus in patients with established left ventricular systolic dysfunction and symptoms of HF. The lack of such data is noteworthy, both because the progression of HF is frequently associated with decreases in blood pressure (due to deterioration of cardiac performance) and decreases in serum lipids (due to development of cardiac cachexia) (421) and because the benefits of drugs used to lower blood pressure or blood lipids may be seen only during prolonged periods of treatment, *i.e.*, those that exceed the expected life span of many patients with HF (33;34;45;421;422). Nevertheless, it is prudent to manage hypertension, hypercholesterolemia, and diabetes mellitus in patients with HF as if the patients did not have HF. This may be particularly true in patients with HF and preserved systolic function who may respond particularly well to treatments that lower blood pressure (430;431).

Drugs that can both control blood pressure and treat HF should be preferred in patients with both conditions; this includes the use of diuretics, ACE inhibitors, and beta-blockers. In contrast, physicians should avoid the use of most calcium channel blockers, because of their cardiodepressant

effects, or potent direct-acting vasodilators such as minoxidil, because of their sodium retaining effects.

The drugs routinely used in the management of HF in nondiabetic patients should be administered to those with diabetes, because ACE inhibitors and beta-blockers prevent the progression of HF in diabetic patients as well as in nondiabetic patients (143;176;432). Physicians should not avoid the use of beta-blockers in diabetic patients despite fears that these drugs may mask symptoms of hypoglycemia produced by antidiabetic therapy or may exacerbate glucose intolerance or insulin resistance.

b. Coronary Artery Disease

Approximately two thirds of patients with HF have underlying coronary artery disease, which may limit exercise tolerance by causing angina pectoris or may lead to further myocardial injury by causing a myocardial infarction. Therefore, physicians should manage both the symptomatic and prognostic consequences of the patient's underlying coronary artery disease.

RECOMMENDATIONS CONCERNING MANAGEMENT OF PATIENTS WITH ANGINA PECTORIS. In general, patients who have both angina pectoris and HF should be given drugs that relieve angina along with drugs that are appropriate in the management of HF (433). Both nitrates and beta-blockers can improve anginal symptoms and may produce hemodynamic and clinical benefits in patients with left ventricular systolic dysfunction, and thus, they are preferred if both conditions coexist (174-176;434;435). Yet, the combination of the 2 drugs may produce little improvement in anginal pain unless fluid retention is adequately controlled with diuretics. It is therefore noteworthy that the decrease in ventricular volume and pressures produced by diuretics may exert independent antianginal effects (436).

Some have suggested that the systemic and coronary vasodilator actions of calcium channel blockers might improve cardiac performance and relieve myocardial ischemia, but these theoretical advantages have not been translated into clinical benefits in controlled clinical trials in HF (437-439). These drugs have not improved symptoms of HF or enhanced exercise tolerance (436-440), and short- and long-term treatment with these drugs (even the use of sustained-release or vasoselective preparations) has increased the risk of worsening HF and death in patients with left ventricular dysfunction (441-450). Therefore, most calcium channel blockers should be avoided in patients with HF, even when used for the treatment of angina or hypertension. Of available agents, only amlodipine has been shown not to adversely affect survival, although experience with the drug exists largely in patients who are not taking beta-blockers (451).

In patients with both HF and angina pectoris, strong consideration should be given to the use of coronary revascularization. Coronary revascularization can relieve symptoms of myocardial ischemia (452;453), and coronary artery bypass

surgery has been shown to lessen angina and reduce the risk of death in patients who have multivessel disease, systolic dysfunction, and stable angina (454) [see the ACC/AHA/ACP-ASIM Guidelines for the Management of Patients With Chronic Stable Angina (455) or the ACC/AHA Guidelines for Coronary Artery Bypass Graft Surgery (16)].

RECOMMENDATIONS CONCERNING MANAGEMENT OF PATIENTS WITHOUT ANGINA. In patients with a prior myocardial infarction but without HF or angina, 3 types of interventions have been used to reduce the risk of reinfarction and death: neurohormonal antagonists such as ACE inhibitors and beta-blockers (41;56;57;62); antiplatelet drugs such as aspirin and clopidogrel (152;154); and coronary revascularization (452). In patients who have had a myocardial infarction and who have HF but not angina, the use of ACE inhibitors and beta-blockers can also decrease the risk of reinfarction and death (59-61;456;457), but it is less clear whether such patients benefit from the use of aspirin or revascularization.

Aspirin has been shown to reduce the risk of major cardiovascular events in patients without HF, but its ability to do so in patients with HF has not been established (152), and concerns have been raised that aspirin may attenuate the hemodynamic and prognostic benefits of ACE inhibitors (130-132). For these reasons, the role of aspirin in preventing ischemic events in patients with chronic HF is controversial. Alternative antiplatelet agents (e.g., clopidogrel) may not interact adversely with ACE inhibitors (151) and may have superior effects in preventing clinical events (154), but their ability to favorably affect outcomes in HF has not been demonstrated. (See section on ACE inhibitors.)

Some physicians recommend the use of coronary revascularization in patients with HF and coronary artery disease who do not have symptoms of angina. Advocates of this approach have suggested that surgical reperfusion can improve cardiac function and relieve symptoms of HF in patients with viable but impaired myocardium (458-460) and may also reduce the risk of a fatal coronary occlusion in patients with established multivessel disease (459). Despite these theoretical possibilities, however, coronary revascularization has not been shown to improve cardiac function or symptoms or to prevent reinfarction or death in patients with HF and no angina (15;461).

c. Supraventricular Arrhythmias

The course of patients with HF is frequently complicated by supraventricular tachyarrhythmias, which may occur when the myocardial disease process affects the atria or when the atria are distended as a result of pressure or volume overload of the right or left ventricles. The most common atrial arrhythmia is atrial fibrillation, which affects 10% to 30% of patients with chronic HF and is associated with a reduction in exercise capacity and a worse long-term prognosis (462-464).

Supraventricular tachyarrhythmias may exert adverse effects by 3 different mechanisms: the stasis of blood in the atria may predispose patients to pulmonary or systemic

emboli; the loss of atrial enhancement of ventricular filling may compromise cardiac output; and the rapidity of ventricular response may diminish both cardiac contraction (by aggravating abnormalities of the force-frequency relation) (465;466) and cardiac relaxation (by shortening ventricular filling time) (467;468). In most patients with an ischemic or nonischemic dilated cardiomyopathy, the rapidity of ventricular response is more important than the loss of atrial support, because restoration of sinus rhythm does not result in predictable clinical benefits (469). Rapid supraventricular arrhythmias may actually cause a cardiomyopathy (even in patients without an underlying contractile abnormality) or may exacerbate a cardiomyopathy caused by another disorder (49;50). Hence, the control of ventricular rate and the prevention of thromboembolic events are essential elements of the treatment of HF in patients with an underlying supraventricular arrhythmia (470;471).

RECOMMENDATIONS CONCERNING MANAGEMENT. The agent most commonly used in clinical practice to slow the ventricular response in patients with HF and atrial fibrillation is digoxin, but the cardiac glycoside slows atrioventricular conduction primarily at rest and not during exercise (207;472). Hence, digitalis does not block the excessive exercise-induced tachycardia that may limit the functional capacity of patients with HF (205-207;472). Beta-blockers are more effective than digoxin during exercise (205;207) and are preferred because of their favorable effects on the natural history of HF (174-176). Although both verapamil and diltiazem can also suppress the ventricular response during exercise, they can depress myocardial function and increase the risk of HF and thus should be avoided (444;447). If beta-blockers are ineffective or contraindicated in patients with atrial fibrillation and HF, amiodarone may be a useful alternative (473). Atrioventricular nodal ablation may be needed if tachycardia persists despite pharmacological therapy (474). Regardless of the intervention used, every effort should be made to reduce the ventricular response to less than 80 to 90 beats per min at rest and less than 110 to 130 beats per min during moderate exercise. Control of ventricular rate should be combined with the use of warfarin, which has been shown to reduce the risk of thromboembolic events in patients with atrial fibrillation (471).

Should patients with HF and atrial fibrillation be converted to and maintained in sinus rhythm? Although atrial fibrillation increases the risk of embolic events, the benefits of restoring sinus rhythm remain unclear (471), and the difficulties and risks of doing so should not be underestimated. Most patients who are electrically converted to sinus rhythm will revert to atrial fibrillation within a short time, unless they are treated with a class I or III antiarrhythmic drug (462). However, patients with HF are not likely to respond favorably to Class I drugs and may be particularly predisposed to their cardiodepressant and proarrhythmic effects (74;475), which can increase the risk of death (476-478). Class III anti-arrhythmic agents (e.g., sotalolol, dofetilide, and amiodarone) can maintain sinus rhythm in some patients, but

treatment with these drugs is associated with an increased risk of organ toxicity (amiodarone) (479;480), proarrhythmia (dofetilide) (481), and death (D-sotalol) (482). The long-term use of antiarrhythmic drugs (other than amiodarone) is associated with a worse prognosis when they are administered to patients with HF and atrial fibrillation (483).

The efficacy and safety of restoring and maintaining sinus rhythm in patients with atrial fibrillation is now being evaluated in a large-scale clinical trial. Until this study is completed, restoration of sinus rhythm is most warranted in patients in whom recurrent or sustained atrial arrhythmias are associated with worsening symptoms that can be directly attributed to the loss of atrial transport function.

d. Ventricular Arrhythmias and Prevention of Sudden Death

Patients with HF are at high risk for sudden death, which may occur regardless of the cause of left ventricular systolic dysfunction or the severity of symptoms. Nearly all patients with HF have frequent and complex ventricular arrhythmias, and approximately 50% to 70% of patients with HF have episodes of nonsustained ventricular tachycardia on ambulatory electrocardiographic monitoring. However, it is not clear whether the occurrence of complex ventricular arrhythmias in patients with HF contributes to the high frequency of sudden death, or alternatively, simply reflects the underlying disease process (484-486). Recent studies suggest that sudden death in patients with HF does not generally result from progression of a nonsustained to a sustained ventricular tachyarrhythmia but is frequently due to an acute ischemic event (in patients with underlying coronary artery disease) or to a bradyarrhythmia or electrical-mechanical dissociation (in patients with a nonischemic cardiomyopathy).

Despite these recent findings, many physicians still assume that nonsustained ventricular arrhythmias play a primary role in the occurrence of sudden death and have advocated the routine or selective use of antiarrhythmic interventions in patients with advanced ventricular dysfunction. However, although all antiarrhythmic drugs can suppress ventricular ectopic rhythms in patients with HF, such an action has not led to a reduction in the risk of sudden death in controlled clinical trials (477;478). Furthermore, most antiarrhythmic drugs have negative inotropic effects and can increase the risk of serious arrhythmia; these adverse cardiovascular effects are particularly pronounced in patients with left ventricular systolic dysfunction (74;474;475). This risk is particularly high with the use of Class IA agents (quinidine and procainamide), Class IC agents (flecainide and encainide), and some Class III agents (D-sotalol) (476-478;482).

RECOMMENDATIONS CONCERNING MANAGEMENT. In general, physicians should not use ambulatory electrocardiographic monitoring to detect asymptomatic ventricular arrhythmias in patients with HF, and they should not attempt to treat such arrhythmias if detected. However, they should make every effort to prevent the occurrence of sudden death. Three types

of interventions have been proposed to accomplish this goal: beta-adrenergic blocking drugs, amiodarone, and implantable cardioverter-defibrillators.

Clinical trials with beta-blockers have shown a reduction in sudden death, as well as in all-cause mortality, in both post-infarction patients and patients with HF regardless of origin (57;58;174-176). As a result, patients with HF due to left ventricular systolic dysfunction should routinely undergo long-term treatment with beta-blockers to reduce the risk of sudden death, unless they have a contraindication to their use or have been shown to be unable to tolerate treatment with these drugs. Patients being started on a beta-blocker should have no or minimal evidence of fluid overload and should not have recently required treatment with an intravenous positive inotropic agent.

Amiodarone is a class III antiarrhythmic agent but differs from other drugs in this class in having a sympatholytic effect on the heart (487). In one randomized, open-label trial, amiodarone therapy was associated with a significant reduction in the risk of death (488), but in a second double-blind, randomized trial, amiodarone had little overall effect on all-cause mortality or on the combined risk of death or hospitalization for HF (489), except possibly in patients with a nonischemic cardiomyopathy (490). Interestingly, the benefits of treatment, if any, may not have been related solely to the drug's antiarrhythmic effects, because amiodarone also increased left ventricular ejection fraction and decreased the risk of worsening HF (489;490). The uncertainty of its benefits coupled with its known toxicity has led to considerable controversy regarding the role of amiodarone in the management of HF. Until further trials are completed, the routine use of amiodarone to prevent sudden death is not recommended. At the present time, the drug may be useful primarily in suppressing the recurrence of a lethal ventricular arrhythmia (alone or in conjunction with a beta-blocker and an implantable cardioverter-defibrillator) in patients with a history of sudden death, ventricular fibrillation, or sustained or hemodynamically destabilizing ventricular tachycardia.

Implantation of a cardioverter-defibrillator has been shown to reduce mortality in cardiac arrest survivors, but its role in the primary prevention of sudden death is less clear. Compared with the use of antiarrhythmic drugs, implantation of a defibrillator device improved outcomes in patients with coronary artery disease and a reduced ejection fraction in whom ventricular tachycardia could be induced during electrophysiological testing after the finding of nonsustained ventricular tachycardia on ambulatory monitoring (491). However, these results cannot be extrapolated to the general population of patients with HF, and thus, there is little evidence to justify the routine placement of an implantable cardioverter-defibrillator to prevent sudden death or prolong life in patients with chronic HF who have asymptomatic arrhythmias. Large-scale, long-term trials of defibrillator therapy in a broad population of patients with chronic HF are now ongoing; these trials will not only define the role of these devices but will also determine whether their use adds meaningfully to the reduction in sudden death risk seen when beta-

blockers are used for the treatment of HF. Until such trials are completed, implantable cardioverter-defibrillators should be used primarily to prevent sudden death, alone or in conjunction with a beta-blocker and/or amiodarone, in patients with a history of sudden death or of a sustained or hemodynamically destabilizing ventricular tachycardia or ventricular fibrillation.

e. Prevention of Thrombotic 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 (492;493) and perhaps due to increased activity of procoagulant factors (494). 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 ejection fractions and echocardiographic evidence of intracardiac thrombi (495-499). These rates are sufficiently low to limit the detectable benefit of anticoagulation in these patients.

There are no controlled trials of warfarin or other antithrombotic agents in patients with HF (500). In several retrospective analyses, the risk of thromboembolic events was not lower in patients taking warfarin, than in patients not treated with antithrombotic drugs (495;497;498). 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 (501-503).

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 ejection fractions and dilated hearts (492). Others would advocate the use of warfarin in patients who are known to harbor a cardiac thrombus (493), even though many thrombi detected by echocardiography do not embolize and many embolic events are probably related to thrombi that are not visualized (125;504). Anticoagulation with warfarin is most justified in patients with HF who have experienced a previous embolic event or who have paroxysmal or chronic atrial fibrillation (471). The effects of warfarin and the antiplatelet drugs aspirin and clopidogrel on major clinical events are now being compared in a large-scale trial.

2. Noncardiovascular Disorders

a. Patients With Renal Insufficiency

Patients with HF frequently have impaired renal function as a result of poor renal perfusion, intrinsic renal disease, or drugs used to treat HF. Patients with renal hypoperfusion or intrinsic renal disease show an impaired response to diuretics and ACE inhibitors (108;505) and are at increased risk of adverse effects during treatment with digitalis (215). Renal function may worsen during treatment with diuretics or ACE

inhibitors (107;359), although the changes produced by these drugs are frequently short-lived and generally asymptomatic and reversible. Persistent or progressive renal functional impairment often reflects deterioration of the underlying renal disease process and is associated with a poor prognosis (27;506). The symptoms of HF in patients with end-stage renal disease may be exacerbated by an increase in loading conditions produced both by anemia (507) and by fistulae implanted to permit dialysis.

Despite the potential for these adverse interactions, most patients with HF tolerate mild to moderate degrees of functional renal impairment without difficulty. In these individuals, changes in blood urea nitrogen and serum creatinine are generally clinically insignificant and can be managed without the withdrawal of drugs needed to slow the progression of HF. However, if the serum creatinine increases to more than 3 mg per dL, the presence of renal insufficiency can severely limit the efficacy and enhance the toxicity of established treatments (108;215;505). In patients with a serum creatinine greater than 5 mg per dL, hemofiltration or dialysis may be needed to control fluid retention, minimize the risk of uremia, and allow the patient to respond to and tolerate the drugs routinely used for the management of HF (361;508).

b. Patients With Pulmonary Disease

Because dyspnea is the key symptom in both HF and pulmonary disease, it is important to distinguish the 2 diseases and to quantify the relative contribution of cardiac and pulmonary components to the disability of the patient when both disorders co-exist. Exercise testing with simultaneous gas exchange or blood gas measurements may be helpful in this regard, particularly when used in conjunction with right heart catheterization (509).

Some drugs used to treat HF can produce or exacerbate pulmonary symptoms. ACE inhibitors can cause a persistent nonproductive cough that can be confused with a respiratory infection, and conversely, ACE inhibitors may be inappropriately stopped in patients with pulmonary causes of cough. Therefore, physicians should seek a pulmonary cause in all patients with HF who complain of cough, whether or not they are taking an ACE inhibitor. The cough should be attributed to the ACE inhibitor only if respiratory disorders have been excluded and the cough disappears after cessation of ACE inhibitor therapy and recurs after reinstatement of treatment. Similarly, beta-blockers can aggravate bronchospastic symptoms in patients with asthma, and therefore, all beta-blockers (regardless of their selectivity) should be avoided in patients with reactive airways disease. Both metoprolol and bisoprolol lose their beta-1 selectivity when prescribed in doses that have been associated with an improvement in survival in patients with HF. It is therefore noteworthy that most patients with chronic obstructive pulmonary disease do not have a bronchospastic component to their illness and remain reasonable candidates for beta-blockade (510).

c. Patients With Cancer

Patients with cancer are particularly predisposed to the development of HF as a result of the cardiotoxic effects of many cancer chemotherapeutic agents, especially the anthracyclines (511), high-dose cyclophosphamide (512-516) and trastuzumab (517). Trastuzumab is a monoclonal antibody recently approved for therapy of metastatic breast cancer (518), that has a significant potential to cause HF, especially when combined with anthracyclines. Mediastinal radiation can also cause acute and chronic injury to the pericardium, myocardium, cardiac valves, and coronary arteries, particularly when used in conjunction with cardiotoxic chemotherapy (519).

Patients undergoing potentially cardiotoxic treatments for cancer should be monitored closely for the development of cardiac dysfunction. Although noninvasive assessments of left ventricular function and endomyocardial biopsy have been advocated by some investigators (520), many cases escape early detection despite close surveillance. Dexrazoxane may confer some cardioprotection in patients undergoing anthracycline-based chemotherapy and may allow for higher doses of the chemotherapy to be given (521;522). Heart failure due to chemotherapeutic agents is managed similarly to HF due to other causes, although it is not clear whether patients with cancer respond similarly to patients without cancer. Nevertheless, because most patients with anthracycline-induced cardiomyopathy have striking degrees of tachycardia, many experts believe that beta-blockers play a particularly important role in the management of these patients.

d. Patients With Thyroid Disease

Patients with both hyperthyroidism and hypothyroidism are prone to develop heart failure and, especially in view of the increasing use of amiodarone and resultant amiodarone-induced thyroid dysfunction, surveillance for and aggressive therapy of thyroid disorders in patients with HF is important.

Recommendations for Management of Concomitant Diseases in Patients With HF

Class I

1. Control of systolic and diastolic hypertension in patients with HF in accordance with recommended guidelines. (*Level of Evidence: A*)
2. Nitrates and beta-blockers (in conjunction with diuretics) for the treatment of angina in patients with HF. (*Level of Evidence: B*)
3. Coronary revascularization in patients who have both HF and angina. (*Level of Evidence: A*)
4. Anticoagulants in patients with HF who have paroxysmal or chronic atrial fibrillation or a previous thromboembolic event. (*Level of Evidence: A*)
5. Control of the ventricular response in patients with HF and atrial fibrillation with a beta-blocker (or

amiodarone, if the beta-blocker is contraindicated or not tolerated). (*Level of Evidence: A*)

6. Beta-adrenergic blockade (unless contraindicated) in patients with HF to reduce the risk of sudden death. Patients should have no or minimal fluid retention and should not have recently required treatment with an intravenous positive inotropic agent. (*Level of Evidence: A*)
7. Implantable cardioverter-defibrillator (alone or in combination with amiodarone) in patients with HF who have a history of sudden death, ventricular fibrillation, or hemodynamically destabilizing ventricular tachycardia. (*Level of Evidence: A*)

Class IIa

1. Antiplatelet agents for prevention of myocardial infarction and death in patients with HF who have underlying coronary artery disease. (*Level of Evidence: B*)
2. Digitalis to control the ventricular response in patients with HF and atrial fibrillation. (*Level of Evidence: A*)

Class IIb

1. Coronary revascularization in patients who have HF and coronary artery disease but no angina. (*Level of Evidence: B*)
2. Restoration of sinus rhythm by electrical cardioversion in patients with HF and atrial fibrillation. (*Level of Evidence: C*)
3. Amiodarone to prevent sudden death in patients with HF and asymptomatic ventricular arrhythmias. (*Level of Evidence: B*)
4. Anticoagulation in patients with HF who do not have atrial fibrillation or a previous thromboembolic event. (*Level of Evidence: B or C*)

Class III

1. Routine use of an implantable cardioverter-defibrillator in patients with HF. (*Level of Evidence: C*)
2. Class I or III antiarrhythmic drugs (except amiodarone) in patients with HF for the prevention or treatment of asymptomatic ventricular arrhythmias. (*Level of Evidence: A*)
3. Ambulatory electrocardiographic monitoring for the detection of asymptomatic ventricular arrhythmias. (*Level of Evidence: A*)

VI. DIASTOLIC DYSFUNCTION

A. Identification of Patients

Approximately 20% to 40% of patients with HF have preserved left ventricular systolic function and (in the absence of valvular disease) are believed to have an impairment of ventricular relaxation as the primary mechanism leading to symptoms (523-527). Several recognized myocardial disorders are associated with diastolic dysfunction, including restrictive cardiomyopathy, obstructive and nonobstructive

hypertrophic cardiomyopathy, and infiltrative cardiomyopathies. However, the vast majority of patients who present with HF and normal systolic function do not have an identifiable myocardial disease. Although some of these patients may have a mild degree of concentric hypertrophy on echocardiography, most of the hallmarks of dynamic hypertrophic cardiomyopathy are absent (e.g., cavity obliteration or systolic anterior motion of the mitral valve). Furthermore, the therapeutic principles developed for patients with obstructive hypertrophic cardiomyopathy are not appropriate for most patients with HF and preserved left ventricular systolic function.

Heart failure associated with preserved systolic function is primarily a disease of elderly women, most of whom have hypertension (524). This observation may be related to the fact that aging has a greater impact on diastolic function than on systolic performance (528). 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 active relaxation (due to an increase in afterload). 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), 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 that make women more susceptible than men to the cumulative effects of aging on diastolic function (529).

B. Diagnosis

It is difficult to be precise about the diagnosis of diastolic dysfunction. 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 left ventricular filling pressure in a patient with normal left ventricular volumes and contractility. Noninvasive methods (especially those that rely on Doppler echocardiography) have been developed to assist in the diagnosis of diastolic dysfunction, but these tests have significant limitations, because cardiac filling patterns are readily altered by nonspecific and transient changes in loading conditions in the heart as well as by aging, changes in heart rate, or the presence of mitral regurgitation (530-536).

In practice, the diagnosis of diastolic HF is generally based on the finding of typical symptoms and signs of HF in a patient who is shown to have a normal left ventricular ejection fraction and no valvular abnormalities on echocardiography. Every effort should be made to exclude other possible explanations or disorders that may present in a similar manner (537;538) (Table 4).

C. Principles of Treatment

In contrast to the treatment of HF due to systolic dysfunction, few clinical trials are available to guide the management of patients with HF due to diastolic dysfunction. Although controlled studies have been performed with digitalis, ACE inhibitors, angiotensin receptor antagonists, beta-blockers, and calcium channel blockers in patients with HF who had a normal left ventricular ejection fraction, these trials have been small or have produced inconclusive results (64;539-542). Nevertheless, many patients with diastolic HF are treated with these drugs because of the presence of comorbid conditions (i.e., atrial fibrillation, hypertension, diabetes, and coronary artery disease). In addition, recommendations regarding the use of anticoagulation and antiarrhythmic agents apply to both systolic and diastolic HF.

In the absence of controlled clinical trials, the management of patients with diastolic dysfunction is based on the control of physiological factors (blood pressure, heart rate, blood

Table 4. Differential Diagnosis in a Patient With HF and Preserved Systolic Function

Incorrect diagnosis of HF
Inaccurate measurement of left ventricular ejection fraction
Primary valvular disease
Restrictive (infiltrative) cardiomyopathies
Amyloidosis, sarcoidosis, hemochromatosis
Pericardial constriction
Episodic or reversible left ventricular systolic dysfunction
Severe hypertension, 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

HF indicates heart failure.

volume, and myocardial ischemia) that are known to exert important effects on ventricular relaxation (527).

1. Control of Blood Pressure

Hypertension exerts a deleterious effect on diastolic function by causing both structural and functional changes in the heart. Increases in systolic blood pressure have been shown to slow myocardial relaxation (543), 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 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).

2. Control of Tachycardia

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) can provide symptomatic relief in patients with diastolic dysfunction. The benefits of restoring sinus rhythm in these individuals are less clear, however. Preservation of the atrial contribution to ventricular filling has been cited as an explanation for the lessened severity of HF and the lower risk of death reported in elderly patients with sick sinus syndrome who were atrially paced as compared with those who received only a ventricular pacemaker (544;545). However, these observations may not be relevant for patients who have HF associated with long-standing supraventricular arrhythmias. The presence of systolic or diastolic dysfunction may diminish the efficacy and enhance the toxicity of drugs used to achieve and maintain sinus rhythm.

3. Reduction in Central Blood Volume

Because circulating blood volume is a major determinant of ventricular filling pressure, the use of diuretics may improve breathlessness in patients with diastolic as well as systolic dysfunction.

4. Alleviation of Myocardial Ischemia

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 diastolic function.

Recommendations for Management of HF and Preserved Systolic Function

Class I

1. Control of systolic and diastolic hypertension, in accordance with published guidelines. (*Level of Evidence: A*)
2. Control of ventricular rate in patients with atrial fibrillation. (*Level of Evidence: C*)
3. Diuretics to control pulmonary congestion and peripheral edema. (*Level of Evidence: C*)

Class IIa

Coronary revascularization in patients with coronary artery disease in whom symptomatic or demonstrable myocardial ischemia is judged to be having an adverse effect on diastolic function. (*Level of Evidence: C*)

Class IIb

1. Restoration of sinus rhythm in patients with atrial fibrillation. (*Level of Evidence: C*)
2. Use of beta-adrenergic blocking agents, ACE inhibitors, angiotensin receptor blockers, or calcium antagonists in patients with controlled hypertension to minimize symptoms of HF. (*Level of Evidence: C*)
3. Digitalis to minimize symptoms of HF. (*Level of Evidence: C*)

VII. 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 return to good functional capacity.

Most patients hospitalized with severe HF indicate a preference that resuscitation be performed in the event of a cardiopulmonary arrest. In the largest study of patients hospitalized with HF, only 23% stated they did not wish resuscitation, and 40% of these patients subsequently changed their minds after the hospitalization (546). These frequencies are higher than those seen in other chronic diseases (547), perhaps because patients with HF are more likely to experience extended periods of stability with good quality of life after hospitalization for intensive care. Hospitals are required by

the Patient Self-Determination Act (548) to seek and record information regarding advance directives at the time of admission. Yet, when these have not been addressed in advance, forced contemplation of resuscitation options at the time of admission for worsening HF may heighten patient and family anxiety without revealing true preferences (549). The majority of patients with HF who had not discussed resuscitation during hospitalization indicated that they had not desired such an interaction (546). Furthermore, in one study, the impact of resuscitation preferences on in-hospital outcome was minimal even for patients with HF in intensive care, of whom only 4% experienced cardiac arrests, compared with more than 25% of patients in intensive care units who had other chronic illnesses (550).

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 this time, it is important to understand which aspects of further care the patient wishes to forego. In some cases, the patient may want full care 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 (551). 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. Rapid communications with this team will reduce the conflicts and uncertainties that may arise when patients are first seen in an emergent 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.

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 the relief of symptoms other than pain (552). 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 the use of potent analgesics. Physicians caring for these patients, however, are becoming more comfortable with the prescription of anxiolytics and narcotics to ease distress during the last days.

Traditionally, the utilization of hospice care has required a prediction by a physician of death within 6 months, but this operational policy may be difficult to apply because health care providers are generally unable to accurately predict the end of life in patients with HF. In a large US experience of patients hospitalized in intensive care units with terminal stages of disease, the majority of patients who were identified by broad criteria for hospice care survived the next 6

months despite a prediction to the contrary (553). This discrepancy between predicted and actual survival may be particularly great for patients with HF, which more often than other chronic illnesses is characterized by periods of good quality of life despite the approaching end and which is likely to be terminated by sudden death despite a recent remission of symptoms. Current guidelines and policies (554) need to be revised to allow patients with HF to benefit from the type of care that can be provided through hospice services.

Recommendations for End-of-Life Care

Class I

1. **Ongoing patient and family education regarding prognosis for function and survival.** (*Level of Evidence: C*)
2. **Patient and family education about options for formulating and implementing advance directives.** (*Level of Evidence: C*)
3. **Continuity of medical care between inpatient and outpatient settings.** (*Level of Evidence: C*)
4. **Components of hospice care that are appropriate to the relief of suffering.** (*Level of Evidence: C*)

Class III

Implantation of a cardioverter-defibrillator in patients with class IV symptoms who are not anticipated to experience clinical improvement from available treatments. (*Level of Evidence: C*)

VIII. IMPLEMENTATION OF PRACTICE GUIDELINES

Despite the publication of evidence-based guidelines (91;240;555), the current care of patients with HF remains suboptimal. Numerous studies document underutilization of key processes of care, such as use of ACE inhibitors in patients with decreased systolic function and the measurement of left ventricular ejection fraction (381;556;557). The overall quality of inpatient care for HF as judged by both explicit and implicit standards is variable, with lower quality associated with higher readmission rates and mortality (362;558;559). Many HF admissions may be prevented with good outpatient care (560).

The literature on implementing practice guidelines for patients with HF can be divided into 2 areas: isolated provider interventions and disease-management systems.

A. Isolated Provider Interventions

A recent controlled trial has shown that the simple dissemination of an HF guideline followed by written and verbal reminders about recommended actions was unable to change the treatment of HF in the intensive care unit (561). Indeed, an extensive literature has documented how difficult it is to produce appropriate changes in physician behavior (562-564). Basic physician education and passive dissemination of

guidelines alone are generally insufficient to sustain quality improvement. Chart audit and feedback of results, reminder systems to consider use of specific medicines or tests, and the use of local opinion leaders have had variable results. Multifactorial interventions that simultaneously attack different barriers to change tend to be more successful than isolated efforts. For example, academic detailing, which involves intensive educational outreach visits that incorporate communication and behavioral change techniques, has been effective and is commonly used by pharmaceutical companies (565). Thus, dissemination of a practice guideline must be accompanied by more intensive educational and behavioral interventions to maximize the chances of improving physician practice patterns.

B. Disease-Management Systems

The disease-management approach views HF as a chronic illness that spans the home as well as outpatient and inpatient settings. Most patients have multiple medical, social, and behavioral challenges, and effective care requires a multidisciplinary systems approach that addresses these various difficulties. Heart failure disease-management programs vary in their content, but in general, they include intensive patient education, encouragement of patients to be more aggressive participants in their care, close monitoring of patients through telephone follow-up or home nursing, careful review of medications to improve adherence to evidence-based guidelines, and multidisciplinary care with nurse case management directed by a physician. High-risk patients have usually been chosen for such programs.

Observational studies and randomized controlled trials have shown that disease-management programs can reduce the frequency of hospitalization and can improve quality of life and functional status (90;566). Patients at high risk for clinical deterioration or hospitalization are likely to benefit from disease-management programs and represent those for whom such interventions are most likely to be cost-effective (567). The largest successful randomized controlled trial of disease management targeted elderly patients who had been hospitalized for HF, had a prior history of HF, had 4 or more hospitalizations within 5 years, or had an HF exacerbation caused by an acute myocardial infarction or uncontrolled hypertension (87). Patients randomized to the disease-management program had significantly fewer hospitalizations and a reduced cost of care compared with patients in the control group. However, it is not clear which elements of disease-management programs are crucial for success. In addition, it is not known whether such interventions are feasible in settings with limited resources and personnel and among diverse patient populations.

C. Roles of Generalist Physicians and Cardiologists

Insufficient evidence exists to allow for recommendations about the most appropriate roles for generalist physicians and cardiologists in the care of patients with HF. Several

studies indicate that primary care physicians as a group have less knowledge about HF and adhere to guidelines less closely than cardiologists (568-570). Some studies have noted better patient outcomes in patients cared for by cardiologists than in those cared for by generalist physicians (571;572), whereas another has reported that cardiologists deliver more costly care that is accompanied by a trend towards improved survival (573). Despite these observations, primary care physicians with knowledge and experience in HF should be able to care for most patients with uncomplicated HF. By contrast, patients who remain symptomatic despite basic medical therapy may benefit from care directed by consulting physicians who have special expertise and training in the care of patients with HF.

Do generalist physicians and cardiologists provide similar levels of care for the noncardiac comorbid conditions frequently present in patients with HF? What is the optimal time for referral to a specialist? What is the most effective system of comanagement of patients by generalists and cardiologists? What is the most cost-effective entry point into a disease-management program? Regardless of the ultimate answers to these questions, all physicians and other health care providers must advocate and follow care practices that have been shown to improve patient outcomes. If a physician is not comfortable following a specific recommendation (e.g., the use of beta-blockers), then the physician should refer the patient to someone with expertise in HF. A collaborative model in which generalist and specialist physicians work together to optimize the care of patients with HF is likely to be most fruitful.

Recommendations for Implementing Practice Guidelines

Class I

- 1. Multifactorial interventions that attack different barriers to behavioral change. (Level of Evidence: A)**
- 2. Multidisciplinary disease-management programs for patients at high risk for hospital admission or clinical deterioration. (Level of Evidence: B)**
- 3. Academic detailing or educational outreach visits. (Level of Evidence: A)**

Class IIa

- 1. Chart audit and feedback of results. (Level of Evidence: A)**
- 2. Reminder systems. (Level of Evidence: A)**
- 3. Local opinion leaders. (Level of Evidence: A)**

Class IIb

Multidisciplinary disease management programs for patients at low risk for hospital admission or clinical deterioration. (Level of Evidence: B)

Class III

- 1. Dissemination of guidelines without more intensive behavioral change efforts. (Level of Evidence: A)**
- 2. Basic provider education alone. (Level of Evidence: A)**

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