

ACC/AHA Practice Guidelines

ACC/AHA 2005 Guideline Update for the Diagnosis and Management of Chronic Heart Failure in the Adult

A Report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (Writing Committee to Update the 2001 Guidelines for the Evaluation and Management of Heart Failure)

*Developed in Collaboration With the American College of Chest Physicians and the International
Society for Heart and Lung Transplantation*

Endorsed by the Heart Rhythm Society

WRITING COMMITTEE MEMBERS

Sharon Ann Hunt, MD, FACC, FAHA, *Chair*; William T. Abraham, MD, FACC, FAHA; Marshall H. Chin, MD, MPH, FACP; Arthur M. Feldman, MD, PhD, FACC, FAHA; Gary S. Francis, MD, FACC, FAHA; Theodore G. Ganiats, MD; Mariell Jessup, MD, FACC, FAHA; Marvin A. Konstam, MD, FACC; Donna M. Mancini, MD; Keith Michl, MD, FACP; John A. Oates, MD, FAHA; Peter S. Rahko, MD, FACC, FAHA; Marc A. Silver, MD, FACC, FAHA; Lynne Warner Stevenson, MD, FACC, FAHA; Clyde W. Yancy, MD, FACC, FAHA

TASK FORCE MEMBERS

Elliott M. Antman, MD, FACC, FAHA, *Chair*; Sidney C. Smith, Jr, MD, FACC, FAHA, *Vice Chair*; Cynthia D. Adams, MSN, APRN-BC, FAHA; Jeffrey L. Anderson, MD, FACC, FAHA; David P. Faxon, MD, FACC, FAHA*; Valentin Fuster, MD, PhD, FACC, FAHA, FESC*; Jonathan L. Halperin, MD, FACC, FAHA; Loren F. Hiratzka, MD, FACC, FAHA*; Sharon Ann Hunt, MD, FACC, FAHA; Alice K. Jacobs, MD, FACC, FAHA; Rick Nishimura, MD, FACC, FAHA; Joseph P. Ornato, MD, FACC, FAHA; Richard L. Page, MD, FACC, FAHA; Barbara Riegel, DNSc, RN

*Former Task Force Member

This document was approved by the American College of Cardiology Foundation Board of Trustees in August 2005 and by the American Heart Association Science Advisory and Coordinating Committee in August 2005.

When citing this document, the American Heart Association requests that the following citation format be used: Hunt SA, Abraham WT, Chin MH, Feldman AM, Francis GS, Ganiats TG, Jessup M, Konstam MA, Mancini DM, Michl K, Oates JA, Rahko PS, Silver MA, Stevenson LW, Yancy CW. ACC/AHA 2005 guideline update for the diagnosis and management of chronic heart failure in the adult: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (Writing Committee to Update the 2001 Guidelines for the Evaluation and Management of Heart Failure). American College of Cardiology Web Site. Available at: <http://www.acc.org/clinical/guidelines/failure/index.pdf>.

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Circulation is available at <http://www.circulationaha.org>

DOI: 10.1161/CIRCULATIONAHA.105.167586

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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 as they are introduced and tested in the detection, 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 favorably affect the overall cost of care 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 and charged with examining subject-specific data and writing or updating these 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 are frequency of follow-up and cost-effectiveness. When available, information from studies on cost will be considered; however, review of data on efficacy and clinical out-

comes will constitute the primary basis for preparing recommendations in these guidelines.

The ACC/AHA Task Force on Practice Guidelines makes every effort to avoid any actual, potential, or perceived conflicts of interest that might arise as a result of an outside relationship or personal interest of a member of the writing committee. Specifically, all members of the writing committee, as well as peer reviewers of the document, 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 each meeting, and updated and reviewed by the writing committee as changes occur. Please see Appendix I for author relationships with industry and Appendix II for peer reviewer relationships with industry.

The practice guidelines produced are intended to assist healthcare providers 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. These guideline recommendations reflect a consensus of expert opinion after a thorough review of the available, current scientific evidence and are intended to improve patient care. If these guidelines are used as the basis for regulatory/payer decisions, the ultimate goal is quality of care and serving the patient's best interests. The ultimate judgment regarding care of a particular patient must be made by the healthcare provider 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 American College of Chest Physicians, the International Society for Heart and Lung Transplantation, and the Heart Rhythm Society. The guidelines will be reviewed annually by the ACC/AHA Task Force on Practice Guidelines and will be considered current unless they are updated, revised, or withdrawn from publication. The summary article including recommendations is published in the September 20, 2005 issues of both the *Journal of the American College of Cardiology* and *Circulation*. The full-text guideline is posted on the World Wide Web sites of the ACC (www.acc.org) and the AHA (www.my.american-heart.org). Copies of the full text and the summary article are available from both organizations.

Elliott M. Antman, MD, FACC, FAHA
Chair, ACC/AHA Task Force on Practice Guidelines

1. INTRODUCTION

Heart failure (HF) is a major and growing public health problem in the United States. Approximately 5 million patients in this country have HF, and over 550 000 patients are diagnosed with HF for the first time each year (1). The disorder is the primary reason for 12 to 15 million office visits and 6.5 million hospital days each year (2). From 1990 to 1999, the

annual number of hospitalizations has increased from approximately 810 000 to over 1 million for HF as a primary diagnosis and from 2.4 to 3.6 million for HF as a primary or secondary diagnosis (3). In 2001, nearly 53 000 patients died of HF as a primary cause. The number of HF deaths has increased steadily despite advances in treatment, in part because of increasing numbers of patients with HF due to better treatment and “salvage” of patients with acute myocardial infarctions (MIs) earlier in life (1).

Heart failure is primarily a condition of the elderly (4), and thus the widely recognized “aging of the population” also contributes to the increasing incidence of HF. The incidence of HF approaches 10 per 1000 population after age 65 (1), and approximately 80% of patients hospitalized with HF are more than 65 years old (5). Heart failure is the most common Medicare diagnosis-related group (i.e., hospital discharge diagnosis), and more Medicare dollars are spent for the diagnosis and treatment of HF than for any other diagnosis (6). It has been estimated that in 2005, the total direct and indirect cost of HF in the US will be equal to \$27.9 billion (1).

The ACC and the AHA first published guidelines for the evaluation and management of HF in 1995 and published revised guidelines in 2001 (7). Since that time, a great deal of progress has been made in the development of both pharmacological and nonpharmacological approaches to treatment for this common, costly, disabling, and potentially fatal disorder. The number of available treatments has increased, but this increase has rendered clinical decision making far more complex. The timing and sequence of initiating treatments and the appropriateness of prescribing them in combination are uncertain. The increasing recognition of the existence of clinical HF in patients with a normal ejection fraction (EF) (see Section 4.3.2.1) has also led to heightened awareness of the limitations of evidence-based therapy for this important group of patients. For these reasons, the 2 organizations believed that it was appropriate to reassess and update these guidelines, fully recognizing that the optimal therapy of HF remains a work in progress and that future advances will require that the guideline be updated again.

The writing committee was composed of 15 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. 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 American Academy of Family Physicians, 2 reviewers nominated by the American College of Chest Physicians, 1 reviewer nominated by the American College of Physicians, 4 reviewers nominated by the Heart Failure Society of America, and 1 reviewer nominated by the International Society for Heart and Lung Transplantation. In addition, 9 content reviewers and the following committees reviewed the document: ACC/AHA Committee to Develop Performance Measures

for Heart Failure, ACC/AHA Committee to Revise Guidelines for the Management of Patients With Acute Myocardial Infarction, ACC/AHA/ESC Committee to Update Guidelines on the Management of Patients with Atrial Fibrillation, ACC/AHA Committee to Update Guidelines on Coronary Artery Bypass Graft Surgery, ACC Committee to Develop Data Standards on Heart Failure, AHA Quality of Care and Outcomes Research Interdisciplinary Working Group Steering Committee, and AHA Council on Clinical Cardiology Committee on Heart Failure and Transplantation.

The full-text guidelines are available in 2 versions on the ACC and AHA Web sites: a version that highlights the change in recommendations (i.e., deleted text is struck through; new text is underlined) from the 2001 guideline to the 2005 guideline and a “clean” version that incorporates all changes in the recommendations. (The “track changes” version only highlights changes to the recommendations; it does not show changes to supporting text, tables, or figures.)

In formulating the 2001 document, the writing committee developed a new approach to the classification of HF, one that emphasized both the development and progression of the disease. In doing so, the 2001 document identified 4 stages involved in the development of the HF syndrome. The first 2 stages (A and B) are clearly not HF but are an attempt to help healthcare providers with the early identification of patients who are at risk for developing HF. Stages A and B patients are best defined as those with risk factors that clearly predispose toward the development of HF. For example, patients with coronary artery disease, hypertension, or diabetes mellitus who do not yet demonstrate impaired left ventricular (LV) function, hypertrophy, or geometric chamber distortion would be considered Stage A, whereas patients who are asymptomatic but demonstrate LV hypertrophy (LVH) and/or impaired LV function would be designated as Stage B. Stage C then denotes patients with current or past symptoms of HF associated with underlying structural heart disease (the bulk of patients with HF), and Stage D designates patients with truly refractory HF who might be eligible for specialized, advanced treatment strategies, such as mechanical circulatory support, procedures to facilitate fluid removal, continuous inotropic infusions, or cardiac transplantation or other innovative or experimental surgical procedures, or for end-of-life care, such as hospice.

This classification recognizes that there are established risk factors and structural prerequisites for the development of HF and that therapeutic interventions introduced even before the appearance of LV dysfunction or symptoms can reduce the population morbidity and mortality of HF. This classification system is intended to complement but in no way 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 Stage D. It has been recognized for many years that the NYHA functional classification reflects a subjective assessment by a healthcare provider and can change frequently over short periods of time. It has also been recognized that the treatments used

may not differ significantly across the classes. Therefore, the committee believed that a staging system was needed that would reliably and objectively identify patients during the course of their developing disease and that would be linked to treatments uniquely appropriate at each stage of illness. According to this new staging approach, patients would only be expected to either not advance at all or to advance from one stage to the next, unless progression of the disease was slowed or stopped by treatment, and spontaneous reversal of this progression would be considered unusual. For instance, although symptoms (NYHA class) might vary widely over time (in response to therapy or to progression of disease) in a patient who has already developed the clinical syndrome of HF (Stage C), the patient could never return to Stage B (never had HF), and therapies recommended for Stage C will be appropriate even if this patient is in NYHA class I. This new classification scheme adds a useful dimension to our thinking about HF that is similar to that achieved by staging or risk assessment systems for other disorders (e.g., those used in the approach to cancer).

Classification of Recommendations and Level of Evidence are expressed in the ACC/AHA format as follows and described in more detail in Table 1.

Classification of Recommendations

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

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

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/treatment is not useful/effective and in some cases may be harmful.

Level of Evidence

- Level of Evidence A: Data derived from multiple randomized clinical trials or meta-analyses.
- Level of Evidence B: Data derived from a single randomized trial, or nonrandomized studies.
- Level of Evidence C: Only consensus opinion of experts, case studies, or standard-of-care.

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. Recommendations relevant to a class of drugs specify the use of the drugs shown to be effective in clinical trials unless there is reason to believe that such drugs have a broad class effect.

The committee elected to focus this document on the prevention of HF and on the diagnosis and management of chronic HF in the adult patient with normal or low LVEF. 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 ST-Elevation Myocardial Infarction (8) and the ACC/AHA 2003 Update of the Guidelines for the Management of Unstable Angina and Non-ST Elevation Myocardial Infarction (9). 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 the Management of Patients With Valvular Heart Disease (10)] 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 healthcare providers 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 healthcare provider in light of all of the circumstances that are relevant to that patient. These guidelines do not address cost-effectiveness from a societal perspective. The guidelines are not meant to assist policy makers faced with the necessity to make decisions regarding the allocation of finite healthcare resources. In fact, these guidelines assume no resource limitation. They do not provide policy makers with sufficient information to be able to choose wisely between options for resource allocation. 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.

2. CHARACTERIZATION OF HF AS A CLINICAL SYNDROME

2.1. Definition of HF

Heart failure is a complex clinical syndrome that can result from any structural or functional cardiac disorder that

Table 1. Applying Classification of Recommendations and Level of Evidence “Size of Treatment Effect”

	Class I <i>Benefit >>> Risk</i>	Class IIa <i>Benefit >> Risk</i> <i>Additional studies with focused objectives needed</i>	Class IIb <i>Benefit ≥ Risk</i> <i>Additional studies with broad objectives needed; Additional registry data would be helpful</i>	Class III <i>Risk ≥ Benefit</i> <i>No additional studies needed</i>
Level A <i>Multiple (3-5) population risk strata evaluated*</i> <i>General consistency of direction and magnitude of effect</i>	Procedure/Treatment SHOULD be performed/administered <ul style="list-style-type: none"> • Recommendation that procedure or treatment is useful/effective • Sufficient evidence from multiple randomized trials or meta-analyses 	IT IS REASONABLE to perform procedure/administer treatment <ul style="list-style-type: none"> • Recommendation in favor of treatment or procedure being useful/effective • Some conflicting evidence from multiple randomized trials or meta-analyses 	Procedure/Treatment MAY BE CONSIDERED <ul style="list-style-type: none"> • Recommendation’s usefulness/efficacy less well established • Greater conflicting evidence from multiple randomized trials or meta-analyses 	Procedure/Treatment should NOT be performed/administered SINCE IT IS NOT HELPFUL AND MAY BE HARMFUL <ul style="list-style-type: none"> • Recommendation that procedure or treatment not useful/effective and may be harmful • Sufficient evidence from multiple randomized trials or meta-analyses
Level B <i>Limited (2-3) population risk strata evaluated*</i>	Recommendation that procedure or treatment is useful/effective <ul style="list-style-type: none"> • Limited evidence from single randomized trial or non-randomized studies 	Recommendation in favor of treatment or procedure being useful/effective <ul style="list-style-type: none"> • Some conflicting evidence from single randomized trial or non-randomized studies 	Recommendation’s usefulness/efficacy less well established <ul style="list-style-type: none"> • Greater conflicting evidence from single randomized trial or non-randomized studies 	Recommendation that procedure or treatment not useful/effective and may be harmful <ul style="list-style-type: none"> • Limited evidence from single randomized trial or non-randomized studies
Level C <i>Very limited (1-2) population risk strata evaluated*</i>	Recommendation that procedure or treatment is useful/effective <ul style="list-style-type: none"> • Only expert opinion, case studies, or standard-of-care 	Recommendation in favor of treatment or procedure being useful/effective <ul style="list-style-type: none"> • Only diverging expert opinion, case studies, or standard-of-care 	Recommendation’s usefulness/efficacy less well established <ul style="list-style-type: none"> • Only diverging expert opinion, case studies, or standard-of-care 	Recommendation that procedure or treatment not useful/effective and may be harmful <ul style="list-style-type: none"> • Only expert opinion, case studies, or standard-of-care
Suggested phrases for writing recommendations †	should is recommended is indicated is useful/effective/beneficial	is reasonable can be useful/effective/ beneficial is probably recommended or indicated	may/might be considered may/might be reasonable usefulness/efficacy is unknown /unclear/uncertain or not well established	is not recommended is not indicated should not is not useful/effective/beneficial may be harmful

*Data available from clinical trials or registries about the usefulness/efficacy in different sub-populations, such as gender, age, history of diabetes, history of prior MI, history of heart failure, and prior aspirin use.

†In 2003, the ACC/AHA Task Force on Practice Guidelines developed a list of suggested phrases to use when writing recommendations. All recommendations in this guideline have been written in full sentences that express a complete thought, such that a recommendation, even if separated and presented apart from the rest of the document (including headings above sets of recommendations), would still convey the full intent of the recommendation. It is hoped that this will increase readers’ comprehension of the guidelines and will allow queries at the individual recommendation level.

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 LV myocardial function. Heart failure may be associated with a wide spectrum of LV functional abnormalities, which may range from patients with normal LV size and preserved EF to those with severe dilatation and/or markedly reduced EF. In most patients, abnormalities of systolic and diastolic dysfunction coexist, regardless of EF. Patients with normal EF may have a different natural history and may require different treatment strategies than patients with reduced EF, although such differences remain controversial (see Section 4.3.2.1).

Coronary artery disease, hypertension, and dilated cardiomyopathy are the causes of HF in a substantial proportion of patients in the Western world. As many as 30% of patients with dilated cardiomyopathy may have a genetic cause (11). Valvular heart disease is still a common cause of HF. In fact, nearly any form of heart disease may ultimately lead to the HF syndrome.

It should be emphasized that HF is not equivalent to cardiomyopathy or to LV dysfunction; these latter terms describe possible structural or functional reasons for the development of HF. Instead, HF is defined as a clinical syndrome that is characterized by specific symptoms (dyspnea and fatigue) in the medical history and signs (edema, rales) on the physical examination. There is no single diagnostic test for HF because it is largely a clinical diagnosis that is based on a careful history and physical examination.

2.2. Heart Failure 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 either favorable or adverse effects on functional capacity in the absence of measurable changes in ventricular function. Some patients may demonstrate remarkable recovery, sometimes associated with improvement in structural and functional abnormalities. Usually, sustained improvement is associated with drug therapy, and that therapy should be continued indefinitely.

The mechanisms responsible for the exercise intolerance of patients with chronic HF have not been defined clearly. Although HF is generally regarded as a hemodynamic disorder, many studies have indicated that there is a poor relation between measures of cardiac performance and the symptoms produced by the disease. Patients with a very low EF (see Section 4.3.2.1) may be asymptomatic, whereas patients with preserved LVEF may have severe disability. The apparent discordance between EF 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, cardiac rhythm, conduction abnormalities, and right ventricular function (11). In addition, in ambulatory patients, many noncardiac factors may contribute substantially to exercise intolerance. These factors include but are not limited to changes in peripheral vascular function, skeletal muscle physiology, pulmonary dynamics, neurohormonal and reflex autonomic activity, and renal sodium handling. 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.

2.3. Heart Failure 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 and structure of the LV, such that the chamber dilates and/or hypertrophies and becomes more spherical—a process referred to as cardiac remodeling. This change in chamber size and structure not only increases the hemodynamic stresses on the walls of the failing heart and depresses its mechanical performance but may also increase 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 substantially to worsening of symptoms despite treatment. Progression of coronary artery disease, diabetes mellitus, hypertension, or the onset of atrial fibrillation may also contribute to the progression of HF. The development of structural abnormalities can have 1 of 3 outcomes: 1) patients die

before developing symptoms (in Stage A or B), 2) patients develop symptoms controlled by treatment, or 3) patients die of progressive HF. Sudden death can interrupt this course at any time.

Although several factors can accelerate the process of LV remodeling, there is substantial evidence that the activation of endogenous neurohormonal systems plays 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. Neurohormonal activation also has direct deleterious effects on the myocytes and interstitium, altering the performance and phenotype of these cells.

The development of HF can be appropriately characterized by considering 4 stages of the disease, as described in the Introduction. This staging system recognizes that HF, like

coronary artery disease, has established risk factors and structural prerequisites; that the development of HF has asymptomatic and symptomatic phases; and that specific treatments targeted at each stage can reduce the morbidity and mortality of HF (Figure 1).

3. INITIAL AND SERIAL CLINICAL ASSESSMENT OF PATIENTS PRESENTING WITH HF

Recommendations for the Initial Clinical Assessment of Patients Presenting With HF

Class I

1. A thorough history and physical examination should be obtained/performed in patients presenting with HF to identify cardiac and noncardiac disorders or behaviors that might cause or accelerate the development or progression of HF. (Level of Evidence: C)
2. A careful history of current and past use of alcohol, illicit drugs, current or past standard or “alternative therapies,” and chemotherapy drugs should be obtained from patients presenting with HF. (Level of Evidence: C)

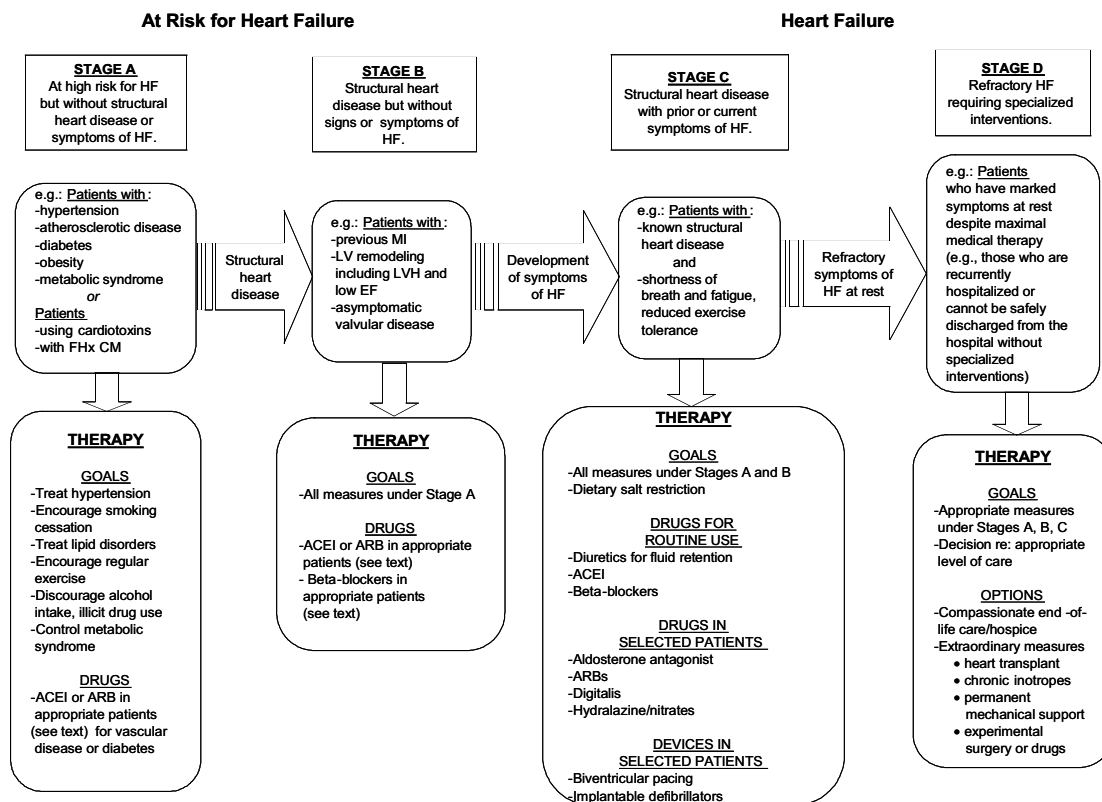


Figure 1. Stages in the development of heart failure/recommended therapy by stage. FHx CM indicates family history of cardiomyopathy; ACEI, angiotensin converting enzyme inhibitors; and ARB, angiotensin receptor blocker.

3. In patients presenting with HF, initial assessment should be made of the patient's ability to perform routine and desired activities of daily living. (*Level of Evidence: C*)
4. Initial examination of patients presenting with HF should include assessment of the patient's volume status, orthostatic blood pressure changes, measurement of weight and height, and calculation of body mass index. (*Level of Evidence: C*)
5. Initial laboratory evaluation of patients presenting with HF should include complete blood count, urinalysis, serum electrolytes (including calcium and magnesium), blood urea nitrogen, serum creatinine, fasting blood glucose (glycohemoglobin), lipid profile, liver function tests, and thyroid-stimulating hormone. (*Level of Evidence: C*)
6. Twelve-lead electrocardiogram and chest radiograph (PA and lateral) should be performed initially in all patients presenting with HF. (*Level of Evidence: C*)
7. Two-dimensional echocardiography with Doppler should be performed during initial evaluation of patients presenting with HF to assess LVEF, LV size, wall thickness, and valve function. Radionuclide ventriculography can be performed to assess LVEF and volumes. (*Level of Evidence: C*)
8. Coronary arteriography should be performed in patients presenting with HF who have angina or significant ischemia unless the patient is not eligible for revascularization of any kind. (*Level of Evidence: B*)

Class IIa

1. Coronary arteriography is reasonable for patients presenting with HF who have chest pain that may or may not be of cardiac origin who have not had evaluation of their coronary anatomy and who have no contraindications to coronary revascularization. (*Level of Evidence: C*)
2. Coronary arteriography is reasonable for patients presenting with HF who have known or suspected coronary artery disease but who do not have angina unless the patient is not eligible for revascularization of any kind. (*Level of Evidence: C*)
3. Noninvasive imaging to detect myocardial ischemia and viability is reasonable in patients presenting with HF who have known coronary artery disease and no angina unless the patient is not eligible for revascularization of any kind. (*Level of Evidence: B*)
4. Maximal exercise testing with or without measurement of respiratory gas exchange and/or blood oxygen saturation is reasonable in patients presenting with HF 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 is reasonable to identify high-risk patients presenting with HF who are candidates for cardiac transplantation or other advanced treatments. (*Level of Evidence: B*)

6. Screening for hemochromatosis, sleep-disturbed breathing, or human immunodeficiency virus is reasonable in selected patients who present with HF. (*Level of Evidence: C*)
7. Diagnostic tests for rheumatologic diseases, amyloidosis, or pheochromocytoma are reasonable in patients presenting with HF in whom there is a clinical suspicion of these diseases. (*Level of Evidence: C*)
8. Endomyocardial biopsy can be useful in patients presenting with HF when a specific diagnosis is suspected that would influence therapy. (*Level of Evidence: C*)
9. Measurement of B-type natriuretic peptide (BNP)* can be useful in the evaluation of patients presenting in the urgent care setting in whom the clinical diagnosis of HF is uncertain. (*Level of Evidence: A*)

Class IIb

1. Noninvasive imaging may be considered to define the likelihood of coronary artery disease in patients with HF and LV dysfunction. (*Level of Evidence: C*)
2. Holter monitoring might be considered in patients presenting with HF who have a history of MI and are being considered for electrophysiologic study to document VT inducibility. (*Level of Evidence: C*)

Class III

1. Endomyocardial biopsy should not be performed in the routine evaluation of patients with HF. (*Level of Evidence: C*)
2. Routine use of signal-averaged electrocardiography is not recommended for the evaluation of patients presenting with HF. (*Level of Evidence: C*)
3. Routine measurement of circulating levels of neurohormones (e.g., norepinephrine or endothelin) is not recommended for patients presenting with HF. (*Level of Evidence: C*)

Recommendations for Serial Clinical Assessment of Patients Presenting With HF

Class I

1. Assessment should be made at each visit of the ability of a patient with HF to perform routine and desired activities of daily living. (*Level of Evidence: C*)
2. Assessment should be made at each visit of the volume status and weight of a patient with HF. (*Level of Evidence: C*)
3. Careful history of current use of alcohol, tobacco, illicit drugs, "alternative therapies," and chemotherapy drugs, as well as diet and sodium intake, should be obtained at each visit of a patient with HF. (*Level of Evidence: C*)

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

Class IIa

Repeat measurement of EF and the severity of structural remodeling can provide useful information in patients with HF 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)

Class IIb

The value of serial measurements of BNP to guide therapy for patients with HF is not well established. (Level of Evidence: C)

3.1. Initial Evaluation of Patients**3.1.1. Identification of Patients**

In general, patients with LV dysfunction or HF present to the healthcare provider 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 healthcare provider to aging, other physiological abnormalities (e.g., deconditioning), or other medical disorders (e.g., pulmonary disease). Therefore, in a patient whose exercise capacity is limited by dyspnea or fatigue, the healthcare provider must determine whether the principal cause is HF or another abnormality. Elucidation of the precise reason for exercise intolerance can be difficult because several 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 2002 Guideline Update for Exercise Testing (12)].

(2) With a syndrome of fluid retention. Patients may present with complaints of leg or abdominal swelling as their 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., abnormal heart sounds or abnormal electrocardiogram or chest X-ray, hypertension or hypotension, diabetes mellitus, an acute MI, an arrhythmia, or a pulmonary or systemic thromboembolic event), patients may be found to have evidence of cardiac enlargement or dysfunction.

3.1.2. Identification of a Structural and Functional 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 MI, 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 comprehensive 2-dimensional echocardiogram coupled with Doppler flow studies to determine whether abnormalities of myocardium, heart valves, or pericardium are present and which chambers are involved. Three fundamental questions must be addressed: 1) is the LVEF preserved or reduced, 2) is the structure of the LV normal or abnormal, and 3) are there other structural abnormalities such as valvular, pericardial, or right ventricular abnormalities that could account for the clinical presentation? This information should be quantified with a numerical estimate of EF, measurement of ventricular dimensions and/or volumes, measurement of wall thickness, and evaluation of chamber geometry and regional wall motion.

Right ventricular size and systolic performance should be assessed. Atrial size should also be determined semiquantitatively and left atrial dimensions and/or volumes measured. All valves should be evaluated for anatomic and flow abnormalities to exclude the presence of primary valve disease. Secondary changes in valve function, particularly the severity of mitral and tricuspid valve insufficiency, should be determined.

Noninvasive hemodynamic data acquired at the time of echocardiography are an important additional correlate for patients with preserved or reduced EF. Combined quantification of the mitral valve inflow pattern, pulmonary venous inflow pattern, and mitral annular velocity provides data about characteristics of LV filling and left atrial pressure. Evaluation of the tricuspid valve regurgitant gradient coupled with measurement of inferior vena caval dimension and its response during respiration provides an estimate of systolic pulmonary artery pressure and central venous pressure. Stroke volume may be determined with combined dimension measurement and pulsed Doppler in the LV outflow tract (13). However, abnormalities can be present in any of these parameters in the absence of HF. No one of these necessarily correlates specifically with HF; however, a totally normal filling pattern argues against clinical HF.

A comprehensive echocardiographic evaluation is important, because it is common for patients to have more than 1 cardiac abnormality that contributes to the development of HF. Furthermore, the study may serve as a baseline for comparison, because measurement of EF and the severity of structural remodeling can provide useful information 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.

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 LV function and right ventricular ejection fraction, but it is unable to directly assess valvular abnormalities or cardiac hypertrophy. Magnetic resonance imaging or computed tomography may be useful in evaluating chamber size and ventricular mass, detecting right ventricular dysplasia, or recognizing the presence of pericardial disease, as well as in assessing cardiac function and wall motion (14). Magnetic resonance imaging may also be used to identify myocardial viability and scar tissue (15). 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 MI, LVH, cardiac conduction abnormality (e.g., left bundle-branch block), or a cardiac arrhythmia. However, because of their low sensitivity and specificity, neither the chest X-ray nor the electrocardiogram should form the primary basis for determining the specific cardiac abnormality responsible for the development of HF.

3.1.3. Evaluation of the Cause of HF

Identification of the condition responsible for the cardiac structural and/or functional abnormalities may be important, because some conditions that lead to LV dysfunction are potentially treatable and/or reversible. Efforts to identify a cause frequently allow the detection of coexistent 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 treatment. Hence, clinicians should focus their efforts on diagnoses that have implications for therapy.

3.1.3.1. History and Physical Examination

Evaluation of potential causative factors begins with a thorough history and careful physical examination (see Table 2). Healthcare providers should inquire about a history of hypertension; diabetes mellitus; dyslipidemia; tobacco use; coronary, valvular, or peripheral vascular disease; rheumatic fever; heart murmur or congenital heart disease; personal or family history of myopathy; mediastinal irradiation; sleep-disturbed breathing; and exposure to cardiotoxic agents, including ephedra, and antineoplastic agents such as anthracyclines, trastuzumab (Herceptin, an antibody for the treatment of breast cancer), or high-dose cyclophosphamide. Heart failure may occur years after exposure to anthracyclines or mediastinal irradiation. Patients should be questioned carefully about illicit drug use, current and past alcohol consumption, symptoms suggestive of sleep-disturbed breathing, 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, obesity, thyroid excess or deficiency, amyloidosis, and pheochromocytoma.

The physical examination should document specific signs of right or left HF, with particular attention to the presence of elevated jugular venous pressure and a third heart sound, because these have been shown to have prognostic significance (16).

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 30% of cases of idiopathic dilated cardiomyopathy may be familial, and polymorphisms in genes encoding cardiac proteins may provide important prognostic information (17). 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.

3.1.3.2. 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

Table 2. Evaluation of the Cause of Heart Failure: The History

History to include inquiry regarding:
Hypertension
Diabetes
Dyslipidemia
Valvular heart disease
Coronary or peripheral vascular disease
Myopathy
Rheumatic fever
Mediastinal irradiation
History or symptoms of sleep-disordered breathing
Exposure to cardiotoxic agents
Current and past alcohol consumption
Smoking
Collagen vascular disease
Exposure to sexually transmitted diseases
Thyroid disorder
Pheochromocytoma
Obesity
Family history to include inquiry regarding:
Predisposition to atherosclerotic disease (Hx of MIs, strokes, PAD)
Sudden cardiac death
Myopathy
Conduction system disease (need for pacemaker)
Tachyarrhythmias
Cardiomyopathy (unexplained HF)
Skeletal myopathies

HF indicates heart failure; Hx, history; MI, myocardial infarction; and PAD, peripheral arterial disease.

count, urinalysis, serum electrolytes (including calcium and magnesium), glycohemoglobin, 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. A fasting transferrin saturation is useful to screen for hemochromatosis; several mutated alleles for this disorder are common in individuals of Northern European descent, and affected patients may show improvement in LV function after treatment with phlebotomy and chelating agents. Magnetic resonance imaging 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 healthcare providers 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. Serum titers of antibodies developed in response to infectious 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, and serum titers of Chagas disease antibodies should be checked in patients with nonischemic cardiomyopathy who have traveled in or immigrated from an endemic region.

Several recent assays have been developed for BNP and related peptides. Several of the natriuretic peptides are synthesized by and released from the heart. Elevated plasma BNP levels have been associated with reduced LVEF (18), LVH, elevated LV filling pressures, and acute MI and ischemia, although they can occur in other settings, such as pulmonary embolism and chronic obstructive pulmonary disease. They are sensitive to other biological factors, such as age, sex, weight, and renal function (19). Elevated levels lend support to a diagnosis of abnormal ventricular function or hemodynamics causing symptomatic HF (20). Trials with this diagnostic marker suggest utility in the urgent-care setting, where it has been used in combination with clinical evaluation to differentiate dyspnea due to HF from dyspnea of other causes (21), and suggest that its use may reduce both the time to hospital discharge and the cost of treatment (22). B-type natriuretic peptide levels tend to be less elevated in HF with preserved EF than in HF with low EF and are lower in obese patients (23, 24). Levels of BNP may be elevated meaningfully in women and in people over 60 years of age who do not have HF, and thus BNP levels should be interpreted cautiously in such individuals when distinguishing between cardiac and noncardiac causes of dyspnea. Elevated BNP levels may lend weight to a suspected diagnosis of HF or trigger consideration of HF when the diagnosis is unknown but should not be used in isolation to confirm or exclude the presence of HF (22, 25).

3.1.3.3. 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 and low EF and also contributes to the progression of HF through mechanisms that include endothelial dysfunction, ischemia, and infarction. Recent cohort studies suggest that there is less often a history of prior MI in patients with HF and preserved EF, although coronary artery disease is often evident on angiography or at autopsy (26-28). 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 modestly reduced EF (variably defined in clinical trials) and angina, although patients with HF or markedly reduced EFs were not included in these studies (21). An ongoing National Institutes of Health-funded trial is evaluating the utility of surgical revascularization in such patients. Because revascularization is recommended in individuals with significant 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 (29).

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 ACC/AHA 2004 Guideline Update for Coronary Artery Bypass Graft Surgery (29) 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 LV 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 (30). Additional studies are needed to determine whether the possibility of myocardial ischemia or viability should be evaluated routinely to assess the contribution of coronary artery disease in patients with HF and reduced LVEF who do not have angina [see the ACC/AHA/ASE 2003 Guideline Update for the Clinical Application of Echocardiography (31) and the ACC/AHA/ASNC Guidelines for Clinical Use of Cardiac Radionuclide Imaging (32)].

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 healthcare providers 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 healthcare providers evaluate patients with HF due to LV 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 (29). Nevertheless, the observation that revascularization might have a favorable effect on LV function has led some experts to suggest that coronary artery disease should be excluded whenever possible, especially in patients with diabetes mellitus or other states associated with silent myocardial ischemia. 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 on noninvasive imaging. In patients in whom coronary artery disease has been excluded previously as the cause of LV dysfunction, repeated invasive or noninvasive assessment for ischemia is generally not indicated unless there is a change in clinical status that suggests the interim development of ischemic disease.

3.1.3.4. Evaluation of the Possibility of Myocardial Disease

One half of patients with HF and low EF have normal or near-normal coronary arteries on coronary angiography, and myocardial disorders are responsible for the development of cardiomyopathy in most such individuals (33). 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., hypertension, diabetes mellitus, hyperthyroidism, hemochromatosis, or hypocalcemia), exposure to a cardiotoxic agent (alcohol, cocaine, methamphetamine, anthracycline, or trastuzumab), or the presence of myocardial inflammation or infiltration.

Although some of these conditions may be detected by endomyocardial biopsy, the overall usefulness of endomyocardial biopsy in the evaluation of patients with a cardiomyopathy of unknown cause is not clear (34). Most patients with a nonischemic cardiomyopathy show nonspecific changes on biopsy (including hypertrophy, cell loss, and

fibrosis), and it has not been established conclusively how biopsy findings (even when positive) affect patient management (35). For example, an endomyocardial biopsy might detect inflammatory cell infiltrates attributed to viral myocarditis in some patients with acute or even chronic HF. Nevertheless, many patients with biopsy-proven myocarditis improve with supportive care only, without specific antiviral or anti-inflammatory treatment; the prognosis of these patients has not been influenced clearly by immunosuppression (36). Similarly, an endomyocardial 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 conclusive evidence that treatment can favorably affect the course of these diseases.

Examples of cases in which a biopsy might be helpful usually occur in a setting in which the cause of the cardiomyopathy is already suspected because of other supportive data. 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 (37, 38). Biopsies can confirm the presence of cardiac disorders that often might weigh against eligibility 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 mechanical circulatory support or immediate heart transplantation (39).

However, endomyocardial biopsy is not indicated in the routine evaluation of cardiomyopathy. Although the risk of a serious complication is less than 1% in centers experienced in this technique, 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 or prognosis and only by operators experienced in its performance.

3.2. Ongoing Evaluation of Patients

Once the nature and cause of the structural abnormalities leading to the development of HF have been defined, healthcare providers 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.

3.2.1. Assessment of Functional Capacity

During the initial and subsequent visits, healthcare providers should inquire about the type, severity, and duration of symp-

toms 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 (40), 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 minutes may have prognostic significance and may help to assess the level of functional impairment in the very sick, but serial changes in walking distance may not parallel changes in clinical status. Maximal exercise testing, with measurement of peak oxygen uptake, has been used to identify appropriate 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.

3.2.2. Assessment of Volume Status

It is critically important for healthcare providers to evaluate the fluid or volume status of patients with HF during the initial visit and each 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 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, healthcare providers should record the patient's body weight and sitting and standing blood pressures and determine the degree of jugular venous distention 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, and scrotum, as well as ascites in the abdomen.

The most reliable sign of volume overload is jugular venous distention (41-43). Right-sided filling pressures are elevated in the basal state or with abdominal compression (hepatojugular reflux) in many patients with chronically ele-

vated left-sided filling pressures (44). Most patients with peripheral edema should also be considered to have volume overload, but 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 rales. This is true even in 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. Indeed, many patients with chronic HF have elevated intravascular volume in the absence of peripheral edema or rales. Studies using ¹³¹I-tagged albumin have demonstrated plasma volume expansion in more than 50% of patients in whom clinical volume overload was not recognized (45). Short-term changes in fluid status are best assessed by measuring changes in body weight; however, changes in body weight may be less reliable during long periods of follow-up, because many patients may gain nonfluid weight and others may lose skeletal muscle mass and body fat as HF progresses due to the development of 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 or abruptly. Clues that suggest the presence of such a marked reduction in cardiac output include narrow pulse pressure, cool extremities, altered mentation, Cheyne-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 the heart and kidney beyond those primarily due to depressed cardiac output (19).

3.2.3. 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 cause fatal arrhythmias and increase the risk of digitalis toxicity, whereas hyperkalemia may complicate therapy with angiotensin converting enzyme (ACE) inhibitors, angiotensin receptor blockers (ARBs), and aldosterone antagonists. Worsening renal function may require adjustment of the doses of diuretics, renin-angiotensin-aldosterone system antagonists, digoxin, and noncardiac medications. Development of hyponatremia or anemia may be a sign of disease progression and is associated with impaired survival.

Serum BNP levels have been shown to parallel the clinical severity of HF as assessed by NYHA class in broad populations. Levels are higher in hospitalized patients and tend to decrease during aggressive therapy for decompensation (see Section 3.1.3.2 on BNP) (20). However, it cannot be assumed that BNP levels can be used effectively as targets for adjustment of therapy in individual patients. Many

patients taking optimal doses of medications continue to show markedly elevated levels of BNP, and some patients demonstrate BNP levels within the normal range despite advanced HF. The use of BNP measurements to guide the titration of drug doses has not been shown to improve outcomes more effectively than achievement of the target doses of drugs shown in clinical trials to prolong life (46). Ongoing trials will help to determine the role of serial BNP measurements in both diagnosis and management of HF.

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 LV 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 (47).

Repeat assessment of EF may be most useful when the patient has demonstrated a major change in clinical status. Both improvement and deterioration may have important implications for future care, although the recommended medical regimen should be continued in most cases. Improvement may reflect recovery from a previous condition, such as viral myocarditis or hypothyroidism, or may occur after titration of recommended therapies for chronic HF. Deterioration may reflect gradual disease progression or a new event, such as recurrent MI. Routine assessment of EF at frequent, regular, or arbitrary intervals is not recommended.

There has been no established role for periodic invasive or noninvasive hemodynamic measurements in the management of HF. Most drugs used for the treatment of HF are prescribed on the basis of their ability to improve symptoms or survival rather than their effect on hemodynamic variables. Moreover, the initial and target doses of these drugs are selected on the basis of experience in controlled trials and are 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 that may cause circulatory instability, such as pulmonary diseases and sepsis. Measurements of cardiac output and pulmonary wedge pressure through a pulmonary artery catheter have also been used in patients with refractory HF to assess pulmonary vascular resistance, a determinant of eligibility for heart transplantation. Cardiac output can also be measured by noninvasive methods.

3.2.4. Assessment of Prognosis

Although both healthcare providers 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. However, some attempt at prognostication in HF may provide better

information for patients and their families to help them appropriately plan for their futures. It also identifies patients in whom cardiac transplantation or mechanical device therapy should be considered.

Multivariate analysis of clinical variables has helped to identify the most significant predictors of survival, and prognostic models have been developed and validated (48). Decreasing LVEF, worsening NYHA functional status, degree of hyponatremia, decreasing peak exercise oxygen uptake, decreasing hematocrit, widened QRS on 12-lead electrocardiogram, chronic hypotension, resting tachycardia, renal insufficiency, intolerance to conventional therapy, and refractory volume overload are all generally recognized key prognostic parameters, although the actual prognostic models incorporating them are not widely used in clinical practice (49, 50). Although elevated circulating levels of neurohormonal factors have also been associated with high mortality rates, the routine assessment of neurohormones such as norepinephrine or endothelin is neither feasible nor helpful in clinical management. Likewise, elevated BNP levels predict higher risk of HF and other events after MI, whereas marked elevation in BNP levels during hospitalization for HF may predict rehospitalization and death. Nonetheless, the BNP measurement has not been clearly shown to supplement careful clinical assessment.

Because treatment of HF has improved over the past 10 years, the older prognostic models need to be revalidated (51), and newer prognostic models may have to be developed. Outcomes have been improved for most high-risk patients, which has resulted in a shift in the selection process for patients referred for heart transplantation (51). Routine use of ambulatory electrocardiographic monitoring, T-wave alternans analysis, heart rate variability measurement, and signal-averaged electrocardiography have not been shown to provide incremental value in assessing overall prognosis, although ambulatory electrocardiographic monitoring can be useful in decision making regarding placement of implantable cardioverter-defibrillators (ICDs) (52).

4. THERAPY

4.1. Patients at High Risk for Developing HF (Stage A)

RECOMMENDATIONS

Class I

1. **In patients at high risk for developing HF, systolic and diastolic hypertension should be controlled in accordance with contemporary guidelines. (Level of Evidence: A)**
2. **In patients at high risk for developing HF, lipid disorders should be treated in accordance with contemporary guidelines. (Level of Evidence: A)**
3. **For patients with diabetes mellitus (who are all at high risk for developing HF), blood sugar should be controlled in accordance with contemporary guidelines. (Level of Evidence: C)**

4. Patients at high risk for developing HF should be counseled to avoid behaviors that may increase the risk of HF (e.g., smoking, excessive alcohol consumption, and illicit drug use). (Level of Evidence: C)
5. Ventricular rate should be controlled or sinus rhythm restored in patients with supraventricular tachyarrhythmias who are at high risk for developing HF. (Level of Evidence: B)
6. Thyroid disorders should be treated in accordance with contemporary guidelines in patients at high risk for developing HF. (Level of Evidence: C)
7. Healthcare providers should perform periodic evaluation for signs and symptoms of HF in patients at high risk for developing HF. (Level of Evidence: C)
8. In patients at high risk for developing HF who have known atherosclerotic vascular disease, healthcare providers should follow current guidelines for secondary prevention. (Level of Evidence: C)
9. Healthcare providers should perform a noninvasive evaluation of LV function (i.e., LVEF) in patients with a strong family history of cardiomyopathy or in those receiving cardiotoxic interventions. (Level of Evidence: C)

Class IIa

1. Angiotensin converting enzyme inhibitors can be useful to prevent HF in patients at high risk for developing HF who have a history of atherosclerotic vascular disease, diabetes mellitus, or hypertension with associated cardiovascular risk factors. (Level of Evidence: A)
2. Angiotensin II receptor blockers can be useful to prevent HF in patients at high risk for developing HF who have a history of atherosclerotic vascular disease, diabetes mellitus, or hypertension with associated cardiovascular risk factors. (Level of Evidence: C)

Class III

Routine use of nutritional supplements solely to prevent the development of structural heart disease should not be recommended for patients at high risk for developing HF. (Level of Evidence: C)

Table 3 describes cardiovascular medications useful for treatment of various stages of HF.

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

Table 3. Cardiovascular Medications Useful for Treatment of Various Stages* of Heart Failure

Drug	Stage A	Stage B	Stage C
Ace Inhibitors			
Benazepril	H	—	—
Captopril	H, DN	Post MI	HF
Enalapril	H, DN	Asymptomatic LVSD	HF
Fosinopril	H	—	HF
Lisinopril	H, DN	Post MI	HF
Moexipril	H	—	—
Perindopril	H, CV Risk	—	—
Quinapril	H	—	HF
Ramipril	H, CV Risk	Post MI	Post MI
Trandolapril	H	Post MI	Post MI
Angiotensin Receptor Blockers			
Candesartan	H	—	HF
Eprosartan	H	—	—
Irbesartan	H, DN	—	—
Losartan	H, DN	CV Risk	—
Olmесartan	H	—	—
Telmisartan	H	—	—
Valsartan	H, DN	Post MI	Post MI, HF
Aldosterone Blockers			
Eplerenone	H	Post MI	Post MI
Spironolactone	H	—	HF
Beta Blockers			
Acebutolol	H	—	—
Atenolol	H	Post MI	—
Betaxolol	H	—	—
Bisoprolol	H	—	HF
Carteolol	H	—	—
Carvedilol	H	Post MI	HF, Post MI
Labetalol	H	—	—
Metoprolol succinate	H	—	HF
Metoprolol tartrate	H	Post MI	—
Nadolol	H	—	—
Penbutolol	H	—	—
Pindolol	H	—	—
Propranolol	H	Post MI	—
Timolol	H	Post MI	—
Digoxin	—	—	HF

*See Figure 1 for explanation of stages of heart failure. CV Risk indicates reduction in future cardiovascular events; DN, diabetic nephropathy; H, hypertension; HF, heart failure and asymptomatic left ventricular dysfunction; Post MI, reduction in heart failure or other cardiac events following myocardial infarction.

4.1.1. Control of Risk

4.1.1.1. Treatment of Hypertension

Elevated levels of diastolic and especially systolic blood pressure are major risk factors for the development of HF (53, 54), and long-term treatment of both systolic and diastolic hypertension has been shown to reduce the risk of HF (55-57). A number of large, controlled studies have quite uni-

formly demonstrated that optimal blood pressure control decreases the risk of new HF by approximately 50% (58). Because approximately one fourth of the American population is hypertensive, and the lifetime risk of developing hypertension in the United States exceeds 75% (59), strategies to control hypertension are certainly a vital part of any effort to prevent HF. The subsequent structural abnormalities that occur in patients with hypertension, including LVH or MI (e.g., Stage B HF), portend an even higher number of adverse cardiovascular outcomes. Left ventricular hypertrophy is an independent cardiovascular risk factor that is as potent as age or systolic blood pressure in predicting MI, stroke, sudden death, or HF (60). In the Framingham Heart Study, hypertension accounted for 39% of HF cases in men and 59% in women (53). In addition, the benefits of treating hypertension in patients who have had a prior MI (Stage B) are even more dramatic, with an 81% reduction in the incidence of HF (56).

Healthcare providers should lower both systolic and diastolic blood pressure in accordance with the recommendations provided in published guidelines, including the most recently published report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure (61); target levels of blood pressure are lower in patients with associated major cardiovascular risk factors, especially those with diabetes mellitus (62, 63). When an antihypertensive regimen is devised, optimal control of blood pressure should remain as the primary goal, with the choice of drugs determined by the concomitant medical problems (e.g., coronary artery disease, diabetes, or renal disease). Diuretic-based antihypertensive therapy has repeatedly been shown to prevent HF in a wide range of target populations (64). ACE inhibitors (ACEIs) and beta-blockers are also effective in the prevention of HF (61), whereas calcium antagonists and alpha-blockers are less effective in preventing HF syndrome (65). However, ACEIs and beta-blockers, as single therapies, are not superior to other antihypertensive drug classes in the reduction of all cardiovascular outcomes. Nevertheless, among patients with diabetes or other cardiovascular complications (66, 67), ACEIs have been most notable with respect to a reduction in the onset of HF and new-onset diabetes. Likewise, compared with placebo, the ARBs losartan (68) and irbesartan (69) significantly reduced the incidence of HF in patients with type 2 diabetes mellitus and nephropathy. Ultimately, an appropriate antihypertensive regimen frequently consists of several drugs used in combination. Although prevention of HF is the focus of these guidelines, overall cardiovascular preventative strategies have also been the subject of published guidelines (70).

4.1.1.2. Treatment of Diabetes

Obesity and insulin resistance are important risk factors for the development of HF (71, 72). The presence of clinical diabetes mellitus markedly increases the likelihood of HF in patients without structural heart disease (73) and adversely affects the outcomes of patients with established HF (74, 75). In a study of patients with type 2 diabetes mellitus more than

50 years of age who had urinary albumin greater than 20 mg per liter, 4% of patients developed HF over the study period, of whom 36% died (76). The occurrence of HF represents a major and adverse prognostic turn in a diabetic patient's life. There is a differential gender effect associated with this risk; diabetes mellitus only modestly increases the risk of HF for men, but it increases the relative risk of HF more than 3-fold among women (53). Healthcare providers should make every effort to control hyperglycemia, although such control has not yet been shown to reduce the subsequent risk of HF. In addition, ACEIs or ARBs 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 (66, 77). Long-term treatment with several ACEIs or ARBs has been shown to decrease the risk of renal disease in diabetic patients (78, 79), and prolonged therapy with the ACEI ramipril has been shown to lower the likelihood of cardiovascular death, MI, and HF (66). Likewise, the use of ARBs in patients with diabetes mellitus and hypertension or LVH has been shown to reduce the incidence of first hospitalization for HF, in addition to having other beneficial effects on renal function (68, 69, 80).

4.1.1.3. Management of the Metabolic Syndrome

The clustering of cardiovascular risk factors in individual patients, termed the metabolic syndrome or syndrome X, includes any 3 of the following criteria: abdominal adiposity, hypertriglyceridemia, low high-density lipoprotein, hypertension, and fasting hyperglycemia. It is estimated that the prevalence of the metabolic syndrome in the United States exceeds 20% of individuals who are at least 20 years of age and 40% of the population over 40 years of age (81). The major adverse consequence of the metabolic syndrome is cardiovascular disease in general and may include an increased incidence of new HF (82). As noted previously, the appropriate treatment of hypertension, diabetes mellitus, and dyslipidemia (83) as they occur in isolation can significantly reduce the development of HF. A number of trials are currently in progress to determine the most effective intervention for patients with the metabolic syndrome.

4.1.1.4. 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 healthcare providers should seek to control vascular risk factors in such patients according to recommended guidelines (70). In one large-scale trial, long-term treatment with an ACEI decreased the risk of the primary end point of cardiovascular death, MI, and stroke in patients with established vascular disease who were without evidence of HF or reduced LVEF at the time of randomization but the incidence of new HF was not a primary or secondary end-point, although it was improved (66). Among patients with established coronary artery disease and no HF, another ACEI significantly reduced incidence of death, MI, or cardiac arrest, but again the incidence of new HF was neither a pri-

mary or secondary endpoint (67). A more recent large trial of ACEI versus placebo failed to show a reduction in the primary composite endpoint, although a post hoc analysis did show some reduction in HF hospitalization (83a). The committee, in reviewing the accruing data, decided to change the level of recommendation for the use of ACEI for Stage A patients from Class I in the 2001 document to Class IIa in this document. 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 MI (83, 84, 84a, 84b).

4.1.1.5. 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, amphetamines, and other illicit drugs. Several epidemiological studies have revealed no correlation between the amount of alcohol ingested and the subsequent development of HF; nevertheless, the Writing Committee strongly believed that any patient with a history of alcohol abuse or with current substantial routine alcohol consumption and new-onset HF without other obvious cause should be counseled to become abstinent. Many HF programs limit alcoholic beverage consumption to no more than 1 alcoholic beverage serving daily for all patients with LV dysfunction, regardless of cause (85, 86). 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 (87) and chemotherapeutic agents such as anthracyclines, immunotherapy such as trastuzumab, or high-dose cyclophosphamide (88-90). 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. Use of ephedra, formerly a common ingredient in over-the-counter weight loss preparations, may contribute to the development of HF as well (91).

4.1.1.6. Other Measures

There is no direct evidence that control of dietary sodium or participation in regular exercise can prevent the development of HF; however, in patients with hypertension or other vascular disease, 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.

4.1.2. Early Detection of Structural Abnormalities

Asymptomatic patients with ventricular dilatation and reduced LVEF carry substantially higher risk for subsequent morbidity and mortality than the general population. It would be desirable to construct cost-effective strategies to identify such patients in the interest of reducing their subsequent risk.

Limited information is available to support the cost-effectiveness of broad population screening. Brain natriuretic peptide levels represent a potential tool for this purpose (92). An analysis of the implications of elevated BNP has suggested that the screening of asymptomatic people over the age of 60 years with this blood test could yield cost-effective improvement in clinical outcomes across the population (93). Certain patients are appropriate targets for more aggressive screening on the basis of characteristics that denote an increase in the risk for structural heart disease. Healthcare professionals should 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) (94, 95). Routine periodic assessment of LV function in other patients is not recommended.

4.2. Patients With Cardiac Structural Abnormalities or Remodeling Who Have Not Developed HF Symptoms (Stage B)

RECOMMENDATIONS

Class I

1. All Class I recommendations for Stage A should apply to patients with cardiac structural abnormalities who have not developed HF. (*Levels of Evidence: A, B, and C as appropriate*)
2. Beta-blockers and ACEIs should be used in all patients with a recent or remote history of MI regardless of EF or presence of HF (see Table 3). (*Level of Evidence: A*)
3. Beta-blockers are indicated in all patients without a history of MI who have a reduced LVEF with no HF symptoms (see Table 3 and text). (*Level of Evidence: C*)
4. Angiotensin converting enzyme inhibitors should be used in patients with a reduced EF and no symptoms of HF, even if they have not experienced MI. (*Level of Evidence: A*)
5. An ARB should be administered to post-MI patients without HF who are intolerant of ACEIs and have a low LVEF. (*Level of Evidence: B*)
6. Patients who have not developed HF symptoms should be treated according to contemporary guidelines after an acute MI. (*Level of Evidence: C*)
7. Coronary revascularization should be recommended in appropriate patients without symptoms of HF in accordance with contemporary guidelines (see ACC/AHA Guidelines for the Management of Patients With Chronic Stable Angina). (*Level of Evidence: A*)
8. Valve replacement or repair should be recommended for patients with hemodynamically significant valvular stenosis or regurgitation and no symptoms of HF in accordance with contemporary guidelines. (*Level of Evidence: B*)

Class IIa

1. **Angiotensin converting enzyme inhibitors or ARBs can be beneficial in patients with hypertension and LVH and no symptoms of HF. (Level of Evidence B)**
2. **Angiotensin II receptor blockers can be beneficial in patients with low EF and no symptoms of HF who are intolerant of ACEIs. (Level of Evidence: C)**
3. **Placement of an ICD is reasonable in patients with ischemic cardiomyopathy who are at least 40 days post-MI, have an LVEF of 30% or less, are NYHA functional class I on chronic optimal medical therapy, and have reasonable expectation of survival with a good functional status for more than 1 year. (Level of Evidence: B)**

Class IIb

Placement of an ICD might be considered in patients without HF who have nonischemic cardiomyopathy and an LVEF less than or equal to 30% who are in NYHA functional class I with chronic optimal medical therapy and have a reasonable expectation of survival with good functional status for more than 1 year. (Level of Evidence: C)

Class III

1. **Digoxin should not be used in patients with low EF, sinus rhythm, and no history of HF symptoms, because in this population, the risk of harm is not balanced by any known benefit. (Level of Evidence: C)**
2. **Use of nutritional supplements to treat structural heart disease or to prevent the development of symptoms of HF is not recommended. (Level of Evidence: C)**
3. **Calcium channel blockers with negative inotropic effects may be harmful in asymptomatic patients with low LVEF and no symptoms of HF after MI (see text in Stage C). (Level of Evidence: C)**

Patients without HF symptoms but who have had an MI or who have evidence of LV remodeling are at considerable risk of developing HF (96, 97). In such patients, the incidence of HF can be decreased by reducing the risk of additional injury and by retarding the evolution and progression of LV remodeling. Initial appropriate measures include those listed as class I recommendations for patients in Stage A (also see Section 5).

As is the case with patients who have no structural heart disease, there is no evidence that the use of nutritional supplements can prevent the development of HF in patients with a recent or remote MI with or without LV remodeling. The aldosterone antagonist eplerenone has been shown to reduce morbidity and mortality in a population of patients with low EF and no HF after MI that has already been treated with ACEIs and beta-blockers (98, 99). Other preventive measures have been addressed in related guidelines (100).

4.2.1. Prevention of Cardiovascular Events**4.2.1.1. Patients With an Acute MI**

In patients who are experiencing an acute MI, the infusion of a fibrinolytic agent or the use of percutaneous coronary intervention can decrease the risk of developing HF (101), and these interventions can reduce the risk of death, especially in patients with a prior myocardial injury (102, 103). Patients with an acute infarction also benefit from the administration of both a beta-blocker and either an ACEI or ARB, which can decrease the risk of reinfarction or death when initiated within days after the ischemic event, especially in patients whose course is complicated by HF (104-110). Combined neurohormonal blockade (beta-blocker and ACEI or ARB) produces additive benefits (111). For recommendations on the treatment of patients with MI, see the ACC/AHA Guidelines for the Management of Patients With ST-Elevation Myocardial Infarction (8).

4.2.1.2. Patients With a History of MI but Normal LVEF

Both hypertension and hyperlipidemia should be treated vigorously in patients with a history of MI, because the benefits of treating these coronary risk factors are particularly marked in patients with a prior ischemic event (55, 56). Patients with a recent MI should also receive treatment with ACEIs and beta-blockers (104, 105, 108, 109, 111), which have been shown to reduce the risk of death when initiated days or weeks after an ischemic cardiac event. Evidence from 2 large-scale studies indicates that prolonged therapy with an ACEI can also reduce the risk of a major cardiovascular event, even when treatment is initiated months or years after MI (66, 67).

4.2.1.3. Patients With Hypertension and LVH

See Section 4.1.1.1.

4.2.1.4. Patients With Chronic Reduction of LVEF but No Symptoms

Long-term treatment with an ACEI has been shown to delay the onset of HF symptoms and decrease the risk of death and hospitalization for HF in asymptomatic patients with reduced LVEF, whether due to a remote ischemic injury or to a non-ischemic cardiomyopathy (97, 112). Although a recent trial investigated patients with low EF and HF at the time of MI, there are no studies that specifically address use of ARBs in asymptomatic patients with reduced LVEF. Given results of studies in symptomatic patients with low EF, ARBs may be an appropriate alternative, particularly in patients who cannot tolerate an ACEI. Furthermore, although controlled clinical trials are lacking, the use of beta-blockers in patients with a low EF and no symptoms (especially those with coronary artery disease) is also recommended (107, 111). In such cases, the same beta-blockers should be used that were employed in the large HF trials.

The use of ICD therapy in patients with chronic reduction of LVEF but no symptoms has been evaluated in one large trial including only patients with ischemic cardiomyopathy. The trials assessing ICD for primary prophylaxis in non-ischemic cardiomyopathy have not included functional class I patients and the efficacy of ICDs in this population as a whole is unknown (112a). The trial involving patients with ischemic cardiomyopathy included a subset of asymptomatic patients post-MI with LVEF 30% or less and there was demonstrated benefit of ICD placement (MADIT-II) in that subset. The findings potentially apply to large numbers of patients and the number needed to treat to have benefit would be great. The writing committee struggled with this issue since guidelines are meant to summarize current science and not take into account economic issues or the societal impact of making a recommendation. However, the committee recognizes that economic impact and societal issues will clearly modulate how these recommendations are implemented.

In contrast, there are no data to recommend the use of digoxin in patients with asymptomatic reduction of LVEF, except in those with atrial fibrillation. Because the only reason to treat such patients is to prevent the progression of HF, and because digoxin has a minimal effect on disease progression in symptomatic patients (113), it is unlikely that the drug would be beneficial in those with no symptoms. Likewise, there are no data to recommend the routine use of calcium channel blockers in patients with asymptomatic reduction of LVEF, but they have not been shown to have adverse effects and may be helpful for concomitant conditions such as hypertension. However, the use of calcium channel blockers with negative inotropic effects is not recommended in asymptomatic patients with EF less than 40% after MI (114).

Healthcare providers 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 healthcare providers 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 (115, 116). Therefore, in patients with a reduced LVEF, every effort should be made to control the ventricular response to these tachyarrhythmias or to restore sinus rhythm (see Section 5.0).

4.2.1.5. Patients With Severe Valvular Disease but No Symptoms

Valve replacement or repair surgery should be considered for patients with severe aortic or mitral valve stenosis or regurgitation, even when ventricular function is impaired (117-120). Long-term treatment with a systemic vasodilator drug may be considered for those with severe aortic regurgitation who are deemed to be poor candidates for surgery. Several studies (121, 122) have suggested that prolonged therapy with hydralazine and nifedipine in patients with severe aortic regurgitation and preserved LV function might act to min-

imize 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 (117)]. There are no long-term studies of vasodilator therapy in patients with severe asymptomatic mitral regurgitation.

4.2.2. Early Detection of HF

As noted, 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 healthcare providers. Hence, patients at risk should be advised to inform their healthcare providers about limitations of exercise tolerance or unexplained fatigue, and healthcare providers should intensify their vigilance for the signs and symptoms of HF in such individuals.

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

4.3.1. Patients With Reduced LVEF

RECOMMENDATIONS

Class I

1. Measures listed as Class I recommendations for patients in stages A and B are also appropriate for patients in Stage C. (*Levels of Evidence: A, B, and C as appropriate*)
2. Diuretics and salt restriction are indicated in patients with current or prior symptoms of HF and reduced LVEF who have evidence of fluid retention (see Table 4). (*Level of Evidence: C*)
3. Angiotensin converting enzyme inhibitors are recommended for all patients with current or prior symptoms of HF and reduced LVEF, unless contraindicated (see Table 3 and text). (*Level of Evidence: A*)
4. Beta-blockers (using 1 of the 3 proven to reduce mortality, i.e., bisoprolol, carvedilol, and sustained release metoprolol succinate) are recommended for all stable patients with current or prior symptoms of HF and reduced LVEF, unless contraindicated (see Table 3 and text). (*Level of Evidence: A*)
5. Angiotensin II receptor blockers approved for the treatment of HF (see Table 3) are recommended in patients with current or prior symptoms of HF and reduced LVEF who are ACEI-intolerant (see text for information regarding patients with angioedema). (*Level of Evidence: A*)
6. Drugs known to adversely affect the clinical status of patients with current or prior symptoms of HF and reduced LVEF should be avoided or withdrawn whenever possible (e.g., nonsteroidal anti-inflammatory

Table 4. Oral Diuretics Recommended for Use in the Treatment of Fluid Retention in Chronic Heart Failure

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

mg indicates milligrams; IV, intravenous.

*Higher doses may occasionally be used with close monitoring.

- drugs, most antiarrhythmic drugs, and most calcium channel blocking drugs; see text). (*Level of Evidence: B*)
- Exercise training is beneficial as an adjunctive approach to improve clinical status in ambulatory patients with current or prior symptoms of HF and reduced LVEF. (*Level of Evidence: B*)
 - An implantable cardioverter-defibrillator is recommended as secondary prevention to prolong survival in patients with current or prior symptoms of HF and reduced LVEF who have a history of cardiac arrest, ventricular fibrillation, or hemodynamically destabilizing ventricular tachycardia. (*Level of Evidence: A*)
 - Implantable cardioverter-defibrillator therapy is recommended for primary prevention to reduce total mortality by a reduction in sudden cardiac death in patients with ischemic heart disease who are at least 40 days post-MI, have an LVEF less than or equal to 30%, with NYHA functional class II or III symptoms while undergoing chronic optimal medical therapy, and have reasonable expectation of survival with a good functional status for more than 1 year. (*Level of Evidence: A*)
 - Implantable cardioverter-defibrillator therapy is recommended for primary prevention to reduce total mortality by a reduction in sudden cardiac death in patients with nonischemic cardiomyopathy who have an LVEF less than or equal to 30%, with NYHA functional class II or III symptoms while undergoing chronic optimal medical therapy, and who have reasonable expectation of survival with a good functional status for more than 1 year. (*Level of Evidence: B*)
 - Patients with LVEF less than or equal to 35%, sinus rhythm, and NYHA functional class III or ambulatory class IV symptoms despite recommended, optimal medical therapy and who have cardiac dyssynchrony, which is currently defined as a QRS duration greater than 0.12 ms, should receive cardiac resynchronization therapy unless contraindicated. (*Level of Evidence: A*)
 - Addition of an aldosterone antagonist is reasonable in selected patients with moderately severe to severe symptoms of HF and reduced LVEF who can be carefully monitored for preserved renal function and normal potassium concentration. Creatinine should be less than or equal to 2.5 mg/dL in men or less than or equal to 2.0 mg/dL in women and potassium should be less than 5.0 mEq/L. Under circumstances where monitoring for hyperkalemia or renal dysfunction is not anticipated to be feasible, the risks may outweigh the benefits of aldosterone antagonists. (*Level of Evidence: B*)
- Class IIa**
- Angiotensin II receptor blockers are reasonable to use as alternatives to ACEIs as first-line therapy for patients with mild to moderate HF and reduced LVEF, especially for patients already taking ARBs for other indications. (*Level of Evidence: A*)
 - Digitalis can be beneficial in patients with current or prior symptoms of HF and reduced LVEF to decrease hospitalizations for HF. (*Level of Evidence: B*)
 - The addition of a combination of hydralazine and a nitrate is reasonable for patients with reduced LVEF

who are already taking an ACEI and beta-blocker for symptomatic HF and who have persistent symptoms. (Level of Evidence: A)

4. Placement of an implantable cardioverter-defibrillator is reasonable in patients with LVEF of 30% to 35% of any origin with NYHA functional class II or III symptoms who are taking chronic optimal medical therapy and who have reasonable expectation of survival with good functional status of more than 1 year. (Level of Evidence: B)

Class IIb

1. A combination of hydralazine and a nitrate might be reasonable in patients with current or prior symptoms of HF and reduced LVEF who cannot be given an ACEI or ARB because of drug intolerance, hypotension, or renal insufficiency. (Level of Evidence: C)
2. The addition of an ARB may be considered in persistently symptomatic patients with reduced LVEF who are already being treated with conventional therapy. (Level of Evidence: B)

Class III

1. Routine combined use of an ACEI, ARB, and aldosterone antagonist is not recommended for patients with current or prior symptoms of HF and reduced LVEF. (Level of Evidence: C)
2. Calcium channel blocking drugs are not indicated as routine treatment for HF in patients with current or prior symptoms of HF and reduced LVEF. (Level of Evidence: A)
3. Long-term use of an infusion of a positive inotropic drug may be harmful and is not recommended for patients with current or prior symptoms of HF and reduced LVEF, except as palliation for patients with end-stage disease who cannot be stabilized with standard medical treatment (see recommendations for Stage D). (Level of Evidence: C)
4. Use of nutritional supplements as treatment for HF is not indicated in patients with current or prior symptoms of HF and reduced LVEF. (Level of Evidence: C)
5. Hormonal therapies other than to replete deficiencies are not recommended and may be harmful to patients with current or prior symptoms of HF and reduced LVEF. (Level of Evidence: C)

4.3.1.1. 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 5.0). In addition, moderate sodium restriction, along with daily measurement of weight, is indicated to permit effective use of lower and safer doses of diuretic drugs, even if overt sodium retention can be controlled by the use of diuretics. Immunization with influenza and pneumococcal vaccines may reduce the risk of a respiratory infection. Although most patients should not participate in heavy labor or exhaustive sports, physical

activity should be encouraged (except during periods of acute exacerbation of the signs and symptoms of HF, or in patients with suspected myocarditis), because restriction of activity promotes physical deconditioning, which may adversely affect clinical status and contribute to the exercise intolerance of patients with HF (123-126).

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

1) Antiarrhythmic agents (127) can exert important cardiodepressant and proarrhythmic effects. Of available agents, only amiodarone and dofetilide (128) have been shown not to adversely affect survival.

2) Calcium channel blockers can lead to worsening HF and have been associated with an increased risk of cardiovascular events (129). Of available calcium channel blockers, only the vasoselective ones have been shown not to adversely affect survival (130, 131).

3) Nonsteroidal anti-inflammatory drugs can cause sodium retention and peripheral vasoconstriction and can attenuate the efficacy and enhance the toxicity of diuretics and ACEIs (132-135). A discussion of the use of aspirin as a unique agent is found later in this section (see Section 4.3.1.2.2.1).

Patients with HF should be monitored carefully for changes in serum potassium, and every effort should be made to prevent the occurrence of either hypokalemia or hyperkalemia, both of which may adversely affect cardiac excitability and conduction and may lead to sudden death (136). Activation of both the sympathetic nervous system and renin-angiotensin systems can lead to hypokalemia (137, 138), and most drugs used for the treatment of HF can alter serum potassium (139). Even modest decreases in serum potassium can increase the risks of using digitalis and antiarrhythmic drugs (136, 140), and even modest increases in serum potassium may prevent the utilization of treatments known to prolong life (141). Hence, many experts believe that serum potassium concentrations should be targeted in the 4.0 to 5.0 mmol per liter range. In some patients, correction of potassium deficits may require supplementation of magnesium and potassium (142). In others (particularly those taking ACEIs alone or in combination with aldosterone antagonists), the routine prescription of potassium salts may be unnecessary and potentially deleterious.

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

cian assistant with special training in the care of patients with HF. Such an approach has been reported to have significant clinical benefits (143-146).

4.3.1.2. *Drugs Recommended for Routine Use*

Most patients with HF should be routinely managed with a combination of 3 types of drugs: a diuretic, an ACEI or an ARB, and a beta-blocker (147). The value of these drugs has been established by the results of numerous large-scale clinical trials, and the evidence supporting a central role for their use is compelling and persuasive. Patients with evidence of fluid retention should take a diuretic until a euvolemic state is achieved, and diuretic therapy should be continued to prevent the recurrence of fluid retention. Even if the patient has responded favorably to the diuretic, treatment with both an ACEI and a beta-blocker should be initiated and maintained in patients who can tolerate them because they have been shown to favorably influence the long-term prognosis of HF. Therapy with digoxin as a fourth agent may be initiated at any time to reduce symptoms, prevent hospitalization, control rhythm, and enhance exercise tolerance.

4.3.1.2.1. **DIURETICS.** Diuretics interfere with the sodium retention of HF by inhibiting the reabsorption of sodium or chloride at specific sites in the renal tubules. Bumetanide, furosemide, and torsemide act at the loop of Henle (thus, they are called loop diuretics), whereas thiazides, metolazone, and potassium-sparing agents (e.g., spironolactone) act in the distal portion of the tubule (148, 149). These 2 classes of diuretics differ in their pharmacological actions. The loop diuretics increase sodium excretion up to 20% to 25% of the filtered load of sodium, enhance free water clearance, and maintain their efficacy unless renal function is severely impaired. In contrast, the thiazide diuretics increase the fractional excretion of sodium to only 5% to 10% of the filtered load, tend to decrease free water clearance, and lose their effectiveness in patients with impaired renal function (creatinine clearance less than 40 ml per min). Consequently, the loop diuretics have emerged as the preferred diuretic agents for use in most patients with HF; however, thiazide diuretics may be preferred in hypertensive HF patients with mild fluid retention because they confer more persistent antihypertensive effects.

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 (150, 151). In these short-term studies, diuretic therapy has led to a reduction in jugular venous pressures, pulmonary congestion, peripheral edema, and body weight, all of which were observed within days of initiation of therapy. In intermediate-term studies, diuretics have been shown to improve cardiac function, symptoms, and exercise tolerance in patients with HF (152-154). There have been no long-term studies of diuretic therapy in HF, and thus, their effects on morbidity and mortality are not known.

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

1) Diuretics produce symptomatic benefits more rapidly than any other drug for HF. They can relieve pulmonary and peripheral edema within hours or days, whereas the clinical effects of digitalis, ACEIs, or beta-blockers may require weeks or months to become apparent (155, 156).

2) Diuretics are the only drugs used for the treatment of HF that can adequately control the fluid retention of HF. Although both digitalis and low doses of ACEIs can enhance urinary sodium excretion (101,102), few patients with HF and a history of fluid retention can maintain sodium balance without the use of diuretic drugs. Attempts to substitute ACEIs for diuretics can lead to pulmonary and peripheral congestion (154).

3) Diuretics should not be used alone in the treatment of Stage C HF. Even when diuretics are successful in controlling symptoms and fluid retention, diuretics alone are unable to maintain the clinical stability of patients with HF for long periods of time (154). The risk of clinical decompensation can be reduced, however, when diuretics are combined with an ACEI and a beta-blocker (157).

4) Appropriate use of diuretics is a key element in the success of other drugs used for the treatment of HF. The use of inappropriately low doses of diuretics will result in fluid retention, which can diminish the response to ACEIs and increase the risk of treatment with beta-blockers (158). Conversely, the use of inappropriately high doses of diuretics will lead to volume contraction, which can increase the risk of hypotension with ACEIs and vasodilators (158, 159) and the risk of renal insufficiency with ACEIs and ARBs (160). Optimal use of diuretics is the cornerstone of any successful approach to the treatment of HF.

PRACTICAL USE OF DIURETIC THERAPY. *Selection of patients.* Diuretics should be prescribed to all patients who have evidence of, and to most patients with a prior history of, fluid retention. Diuretics should generally be combined with an ACEI and a beta-blocker. Few patients with HF will be able to maintain dry weight without the use of diuretics.

PRACTICAL USE OF DIURETIC THERAPY. *Initiation and maintenance.* The most commonly used loop diuretic for the treatment of HF is furosemide, but some patients respond favorably to other agents in this category (such as torsemide) because of superior absorption and longer duration of action (161, 162). In outpatients with HF, therapy is commonly initiated with low doses of a diuretic, and the dose is increased until urine output increases and weight decreases, generally by 0.5 to 1.0 kg daily. Further increases in the dose or frequency (i.e., twice-daily dosing) of diuretic administration may be required to maintain an active diuresis and sustain the loss of weight. The ultimate goal of diuretic treatment is to eliminate clinical evidence of fluid retention, such as jugular venous pressure elevation and peripheral edema. Diuretics are generally combined with moderate dietary sodium restriction (3 to 4 g daily).

If electrolyte imbalances are seen, these should be treated aggressively and the diuresis continued. If hypotension or azotemia is observed before the goals of treatment are achieved, the physician may elect to slow the rapidity of diuresis, but diuresis should nevertheless be maintained until fluid retention is eliminated, even if this strategy results in mild or moderate decreases in blood pressure or renal function, as long as the patient remains asymptomatic. Excessive concern about hypotension and azotemia can lead to the underutilization of diuretics and a state of refractory edema. 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 (163).

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

The response to a diuretic is dependent on the concentration of the drug and the time course of its entry into the urine (148, 149). Patients with mild HF respond favorably to low doses because they absorb diuretics rapidly from the bowel and deliver these drugs rapidly to the renal tubules. However, as HF advances, the absorption of the drug may be delayed by bowel edema or intestinal hypoperfusion, and the delivery of the drug and the response to a given intratubular concentration may be impaired by a decline in renal perfusion and function (164-166). Consequently, the clinical progression of HF is characterized by the need for increasing doses of diuretics.

Patients may become unresponsive to high doses of diuretic drugs if they consume large amounts of dietary sodium, are taking agents that can block the effects of diuretics (e.g., nonsteroidal anti-inflammatory drugs, including cyclo-oxygenase-2 inhibitors) (133, 134, 167), or have a significant impairment of renal function or perfusion (161). Diuretic resistance can generally be overcome by the intravenous administration of diuretics (including the use of continuous infusions) (168), the use of 2 or more diuretics in combination (e.g., furosemide and metolazone) (169-172), or the use of diuretics together with drugs that increase renal blood flow (e.g., positive inotropic agents) (172).

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

Diuretics can cause the depletion of important cations (potassium and magnesium), which can predispose patients to serious cardiac arrhythmias, particularly in the presence of digitalis therapy (173). 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 (149). Potassium deficits can be corrected by the short-term use of potassium supplements or, if severe, by the addition of magnesium supplements (174). Concomitant administration of ACEIs alone or in combination with potassium-retaining agents (such as spironolactone) can prevent electrolyte depletion in most patients with HF who are taking a loop diuretic. When these drugs are prescribed, long-term oral potassium supplementation frequently is not needed and may be deleterious.

Excessive use of diuretics can decrease blood pressure and impair renal function and exercise tolerance (158-160, 175), but hypotension and azotemia may also occur as a result of worsening HF, which may be exacerbated by attempts to reduce the dose of diuretics. If there are no signs of fluid retention, hypotension and azotemia are likely to be related to volume depletion and may resolve after a reduction in diuretic dose. The signs of fluid retention, hypotension and azotemia, are likely to reflect worsening HF and a decline in effective peripheral perfusion. This is an ominous clinical scenario and necessitates considering the measures discussed under Stage D HF.

Tables 4 and 5 illustrate oral and intravenous diuretics recommended for use in the treatment of chronic HF.

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

4.3.1.2.2.1. Angiotensin Converting Enzyme Inhibitors: Angiotensin Converting Enzyme Inhibitors in the Management of HF. It is not clear whether the effects of ACEIs can be explained solely by the suppression of angiotensin II production, because ACE inhibition not only interferes with the renin-angiotensin system but also enhances the action of kinins and augments kinin-mediated prostaglandin production (176-178). In experimental models of HF, ACEIs modify cardiac remodeling more favorably than ARBs (179-182),

Table 5. Intravenous Diuretic Medications Useful for the Treatment of Severe Heart Failure

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

mg indicates milligrams; IV, intravenous.

*Higher doses may occasionally be used with close monitoring.

and this advantage of ACEIs is abolished by the coadministration of a kinin receptor blocker (179, 181). Angiotensin converting enzyme inhibitors have been evaluated in more than 7000 patients with HF who participated in more than 30 placebo-controlled clinical trials (183). All of these trials enrolled patients with reduced LVEF (EF less than 35% to 40%) who were treated with diuretics, with or without digitalis. These trials recruited many types of patients, including women and the elderly, as well as patients with a wide range of causes and severity of LV dysfunction. However, patients with preserved systolic function, low blood pressure (less than 90 mm Hg systolic), or impaired renal function (serum creatinine greater than 2.5 mg per mL) were not recruited or represented a small proportion of patients who participated in these studies.

Analysis of this collective experience indicates that ACEIs can alleviate symptoms, improve clinical status, and enhance the overall sense of well-being of patients with HF (184-195). In addition, ACEIs can reduce the risk of death and the combined risk of death or hospitalization (193-195). These benefits of ACE inhibition were seen in patients with mild, moderate, or severe symptoms and in patients with or without coronary artery disease.

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

In general, ACEIs are used together with a beta-blocker. Angiotensin converting enzyme inhibitors should not be pre-

scribed 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 (154). Angiotensin converting enzyme inhibitors are often preferred over ARBs or direct-acting vasodilators (194, 196) because of the greater experience and weight of evidence in support of their effectiveness.

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

PRACTICAL USE OF ACE INHIBITORS. Initiation and maintenance. Although most of the evidence that supports an effect of ACEIs on the survival of patients with HF is derived from experience with enalapril, the available data suggest that there are no differences among available ACEIs in their effects on symptoms or survival (183). Although some have suggested that drugs in this class may differ in their ability to inhibit tissue ACE, no trial has shown that tissue ACE-inhibiting agents are superior to other ACEIs in any clinical aspect of HF. Nevertheless, in selecting among ACEIs, it is recommended that preference be given to ACEIs that have been shown to reduce morbidity and mortality in clinical tri-

als in HF or post-MI populations (captopril, enalapril, lisinopril, perindopril, ramipril, and trandolapril), because these studies have clearly defined a dose that is effective in modifying the natural history of the disease. Such information is generally lacking for ACEIs that have not been shown to be effective in large-scale studies.

Treatment with an ACEI should be initiated at low doses (see Table 5), followed by gradual increments in dose if lower doses have been well tolerated. Renal function and serum potassium should be assessed within 1 to 2 weeks of initiation of therapy and periodically thereafter, especially in patients with pre-existing hypotension, hyponatremia, diabetes mellitus, or azotemia or in those taking potassium supplements. Because fluid retention can blunt the therapeutic effects and fluid depletion can potentiate the adverse effects of ACE (160, 163), healthcare providers should ensure that patients are being given appropriate doses of diuretics before and during treatment with these drugs. Most patients (85% to 90%) with HF can tolerate short- and long-term therapy with these drugs (193-195).

What dose of an ACEI should physicians try to achieve in patients with HF? In controlled clinical trials that were designed to evaluate survival, the dose of the ACEI was not determined by a patient's therapeutic response but was increased until a target dose was reached (193-195). However, these drugs are commonly prescribed in clinical practice at much lower doses that are similar to those recommended for initiation rather than maintenance of therapy. Which approach should be followed? In the controlled clinical trials of ACEIs, low or intermediate doses were commonly prescribed if higher doses could not be tolerated. In controlled trials with newer agents for HF, intermediate doses rather than high doses of ACEIs were generally used as background therapy. Higher doses of an ACEI were better than low doses in reducing the risk of hospitalization, but they showed similar effects on symptoms and mortality (197, 198). Clinicians should attempt to use doses that have been shown to reduce the risk of cardiovascular events in clinical trials. If these target doses of an ACEI cannot be used or are poorly tolerated, intermediate doses should be used with the expectation that there are likely to be only small differences in efficacy between low and high doses. More importantly, clinicians should not delay the institution of beta-blockers in patients because of a failure to reach target ACEI doses. Once the drug has been titrated to the appropriate dose, patients can generally be maintained on long-term therapy with an ACEI with little difficulty. Although symptoms may improve in some patients within the first 48 hours of therapy with an ACEI, the clinical responses to these drugs are generally delayed and may require several weeks, months, or more to become apparent (155, 184). Even if symptoms do not improve, long-term treatment with an ACEI should be maintained to reduce the risk of death or hospitalization. Abrupt withdrawal of treatment with an ACEI can lead to clinical deterioration and should be avoided (199) in the absence of life-threatening complications (e.g., angioedema).

Every effort should be made to minimize the occurrence of sodium retention or depletion during long-term treatment

with an ACEI, because changes in salt and water balance can exaggerate or attenuate the cardiovascular and renal effects of treatment (160, 163). Fluid retention can minimize the symptomatic benefits of ACE inhibition, whereas fluid loss increases the risk of hypotension and azotemia. The use of an ACEI can also minimize or eliminate the need for long-term potassium supplementation. Nonsteroidal anti-inflammatory drugs can block the favorable effects and enhance the adverse effects of ACEIs in patients with HF and should be avoided (135, 137).

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 (200, 201). As a result, in such patients (particularly those who are responding poorly to diuretic drugs), it may be prudent to interrupt treatment with the ACEI temporarily until the clinical status of the patient stabilizes.

Retrospective analyses of large-scale clinical trials have suggested that aspirin might interfere with the benefits of ACE inhibition in patients with HF by inhibiting kinin-mediated prostaglandin synthesis. In short-term hemodynamic and maximal-exercise studies, aspirin can attenuate the hemodynamic actions of ACEIs in patients with HF (202, 203), an effect not seen with nonaspirin antiplatelet agents (e.g., clopidogrel) (204).

In several multicenter trials, concomitant use of aspirin was associated with a diminution of the effect of ACEIs on survival and on cardiovascular morbidity (205, 206). A recent comprehensive systematic overview of 22 060 patients from 6 long-term randomized trials of ACEIs re-evaluated the issue of the potential detrimental effect of combining aspirin with ACEI therapy. When all of these trials were considered together, the effects of ACEIs were significantly beneficial in patients with and without aspirin therapy. The composite risk reduction was 20% for patients taking aspirin and 29% for those not taking aspirin, a difference that did not reach statistical significance (207). A second retrospective review subsequently also reported no adverse effect of concomitant aspirin use with ACEIs on long-term survival (208). Given these retrospective results, many physicians believe the data justify prescribing aspirin and ACEIs together when there is an indication for use of aspirin. However, these large overviews are subject to varying interpretation. Other physicians would consider not combining aspirin with an ACEI because there are no data to indicate that it can reduce the risk of ischemic events in patients with HF (209, 210), or they might consider the use of an alternative antiplatelet agent such as clopidogrel, which does not interact with ACEIs and which may have superior effects in preventing ischemic events (211). However, clopidogrel does not have an indication for the primary prevention of ischemic events. There may be an important interaction between aspirin and ACEIs, but there is controversy regarding this point, and it requires further study.

PRACTICAL USE OF ACE INHIBITORS. *Risks of treatment.* Most of the adverse reactions of ACEIs can be attributed to the 2

principal pharmacological actions of these drugs: those related to angiotensin suppression and those related to kinin potentiation. Other types of side effects may also occur (e.g., rash and taste disturbances).

Adverse effects related to angiotensin suppression.

1. HYPOTENSION

The most common adverse effects of ACE inhibition in patients with HF are hypotension and dizziness. Blood pressure declines without symptoms in nearly every patient treated with an ACEI, so hypotension is generally a concern only if it is accompanied by postural symptoms, worsening renal function, blurred vision, or syncope. Hypotension is seen most frequently during the first few days of initiation of increments in therapy, particularly in patients with hypovolemia, a recent marked diuresis, or severe hyponatremia (serum sodium concentration less than 130 mmol per liter) (212).

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

2. WORSENING RENAL FUNCTION

In states characterized by reduced renal perfusion (such as HF), glomerular filtration is critically dependent on angiotensin-mediated efferent arteriolar vasoconstriction (213), and ACE inhibition may cause functional renal insufficiency (160). 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) (214). A significant increase in serum creatinine (e.g., greater than 0.3 mg per dL) with the use of ACEIs is observed in 15% to 30% of patients with severe HF (215), but in only 5% to 15% of patients with mild to moderate symptoms (216). The risks are substantially greater if patients have bilateral renal artery stenosis or are taking nonsteroidal anti-inflammatory drugs (134, 137, 217). Renal function usually improves after a reduction in the dose of concomitantly administered diuretics, and thus, these patients can generally be managed without the need to withdraw treatment with the ACEI (160). However, if the dose of diuretic cannot be reduced because the patient has fluid retention, the physician and patient may need to tolerate mild to moderate degrees of azotemia to maintain therapy with the ACEI.

3. POTASSIUM RETENTION

Hyperkalemia can occur during ACE inhibition in patients with HF and may be sufficiently severe to cause cardiac conduction disturbances. In general, hyperkalemia is seen in patients whose renal function deteriorates or who are taking oral potassium supplements or potassium-sparing diuretics, or aldosterone antagonists, especially if they have diabetes mellitus (218).

Adverse effects related to kinin potentiation.

1. COUGH

Cough related to the use of ACEIs is the most common reason for the withdrawal of long-term treatment with these drugs (219); the frequency of cough is approximately 5% to 10% in white patients of European descent and rises to nearly 50% in Chinese patients (220). It is characteristically non-productive, is accompanied by a persistent and annoying "tickle" in the back of the throat, usually appears within the first months of therapy, disappears within 1 to 2 weeks of discontinuing treatment, and recurs within days of rechallenge. Other causes of cough, especially pulmonary congestion, should always be considered, and the ACEI should be implicated only after these have been excluded. Demonstration that the cough disappears after drug withdrawal and recurs after rechallenge with another ACEI strongly suggests that ACE inhibition is the cause of the cough. In a number of studies of ACEI cough, it was found that this symptom did not recur with rechallenge and probably was a coincidental finding. Because of the long-term benefits of ACEIs, physicians should encourage patients to continue taking these drugs if the cough is not severe. Only if the cough proves to be persistent and troublesome should the physician consider withdrawal of the ACEI and the use of alternative medications (e.g., an ARB).

2. ANGIOEDEMA

Angioedema occurs in fewer than 1% of patients taking an ACEI but is more frequent in blacks. Because its occurrence may be life-threatening, the clinical suspicion of this reaction justifies subsequent avoidance of all ACEIs for the lifetime of the patient (219). Angiotensin converting enzyme inhibitors should not be initiated in any patient with a history of angioedema. Although ARBs may be considered as alternative therapy for patients who have developed angioedema while taking an ACEI, there are a number of patients who have also developed angioedema with ARBs and extreme caution is advised when substituting an ARB in a patient who has had angioedema associated with ACEI use (221-223, 223a).

4.3.1.2.2.2. Angiotensin Receptor Blockers. Agents that block these receptors were developed on the rationale that 1) angiotensin II production continues in the presence of ACE inhibition, driven through alternative enzyme pathways, and 2) interference with the renin-angiotensin system without

Table 6. Inhibitors of the Renin-Angiotensin-Aldosterone System and Beta-Blockers Commonly Used for the Treatment of Patients With Heart Failure With Low Ejection Fraction

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

ACE indicates angiotensin converting enzyme; mg, milligrams; and kg, kilograms.

inhibition of kininase would produce all of the benefits of ACEIs while minimizing the risk of their adverse reactions (224). However, it is now known that some of the benefits may be related to the accumulation of kinins (225) rather than to the suppression of angiotensin II formation, whereas some of the side effects of ACEIs in HF are related to the suppression of angiotensin II formation (179-181). Table 6 lists the inhibitors of the renin-angiotensin-aldosterone system and beta-blockers that are commonly used for the treatment of patients with HF with low ejection fraction.

Several ARBs (e.g., candesartan, eprosartan, irbesartan, losartan, telmisartan, olmesartan, 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 ACEIs. Nevertheless, in several placebo-controlled studies, long-term therapy with ARBs produced hemodynamic, neurohormonal, and clinical effects consistent with those expected after interference with the renin-angiotensin system (226-231). In patients with evidence of LV dysfunction early after MI, a recent trial demonstrated that ARBs had a benefit that was not inferior to that of ACEIs without an advantage in terms of tolerability (110). However, the addition of an ARB to an ACEI did not improve outcomes and resulted in more side effects.

For patients unable to tolerate ACEIs because of cough or angioedema, the ARBs valsartan and candesartan (223, 232) have demonstrated benefit by reducing hospitalizations and

mortality. The combination of an ACEI and ARBs may produce more reduction of LV size than either agent alone (233). The addition of ARBs to chronic ACEI therapy caused a modest decrease in hospitalization in 2 studies, with a trend to decreased total mortality in one and no impact on mortality in another (232-234).

Recommendations Concerning ARBs.

Angiotensin converting enzyme inhibitors remain the first choice for inhibition of the renin-angiotensin system in chronic HF, but ARBs can now be considered a reasonable alternative. Candesartan improved outcomes in patients with preserved LVEF who were intolerant of ACEIs in the Candesartan in Heart Failure Assessment of Reduction in Mortality and Morbidity (CHARM) Preserved trial (235). Angiotensin receptor blockers are as likely to produce hypotension, worsening renal function, and hyperkalemia as ACEIs. Although angioedema is much less frequent with ARBs, there are cases of patients who developed angioedema to both ACEIs and later to ARBs (223). There is little information available about the addition of ARBs to therapy with both ACEIs and aldosterone antagonists, but risks of renal dysfunction and hyperkalemia would be further increased. Until further information is available, the routine combined use of all 3 inhibitors of the renin-angiotensin system cannot be recommended.

PRACTICAL USE OF ARBs. *Initiation and maintenance.* When used, angiotensin receptor antagonists should be initiated with the starting doses shown in Table 6. Many of the considerations with ARB are similar to those with initiation of an ACEI, as discussed above. Blood pressure (including postural blood pressure changes), renal function, and potassium should be reassessed within 1 to 2 weeks after initiation and followed closely after changes in dose. Patients with systolic blood pressure below 80 mm Hg, low serum sodium, diabetes mellitus, and impaired renal function merit particular surveillance during therapy with inhibitors of the renin-angiotensin-aldosterone system. Titration is generally achieved by doubling doses. For stable patients, it is reasonable to add therapy with beta-blocking agents before full target doses of either ACEIs or ARBs are reached.

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

4.3.1.2.2.3. Aldosterone Antagonists. Although short-term therapy with both ACEIs and ARBs can lower circulating levels of aldosterone, such suppression may not be sustained during long-term treatment (236). The lack of long-term suppression may be important, because experimental data suggest that aldosterone exerts adverse effects on the structure and function of the heart, independently of and in addition to the deleterious effects produced by angiotensin II (237-243).

Spironolactone is the most widely used aldosterone antagonist. In a large-scale, long-term trial (141), low doses of spironolactone (starting at 12.5 mg daily) were added to ACEI therapy for patients with NYHA class IV HF symptoms or class III symptoms and recent hospitalization. The risk of death was reduced from 46% to 35% (30% relative risk reduction) over 2 years, with a 35% reduction in HF hospitalization and an improvement in functional class. Initial creatinine levels were below 2.0 mg per dL in the dose-ranging pilot trial and below 2.5 mg per dL in the main trial. Potassium replacements were stopped at trial entry, and serum potassium and renal function were followed very closely.

A recent trial investigated the newer aldosterone antagonist eplerenone in patients with LVEF less than or equal to 40% and clinical evidence of HF or diabetes mellitus within 14 days of MI. Mortality was decreased from 13.6% to 11.8% at 1 year. Hyperkalemia occurred in 5.5% of patients treated with eplerenone compared with 3.9% of those given placebo overall and in up to 10.1% versus 4.6% of patients with estimated creatinine clearance less than 50 mL per min (98).

Recommendations Concerning Aldosterone Antagonists.

The addition of low-dose aldosterone antagonists should be considered in carefully selected patients with moderately severe or severe HF symptoms and recent decompensation or

with LV dysfunction early after MI. These recommendations are based on the strong data demonstrating reduced death and rehospitalization in 2 clinical trial populations (98,141). The entry criteria for these trials describe a broader population than was actually enrolled, such that the favorable efficacy/toxicity ratio may not be as applicable to patients at the margins of trial eligibility. For both of these major trials, patients were excluded for a serum creatinine level in excess of 2.5 mg per dL, but few patients were actually enrolled with serum creatinine levels over 1.5 mg per dL. In the trial of patients after MI, there was a significant interaction between serum creatinine and benefit of eplerenone. The average serum creatinine of enrolled patients was 1.1 mg per dL, above which there was no demonstrable benefit for survival.

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

PRACTICAL USE OF ALDOSTERONE ANTAGONISTS. *Selection of patients.* Decisions regarding the selection of patients for aldosterone antagonists reflect the balance between potential benefit to decrease death and hospitalization from HF and potential risks of life-threatening hyperkalemia. Despite this, patients who meet recommended criteria from formal trials may need to be excluded in practice for a recent history of renal dysfunction characterized by higher creatinine, markedly elevated blood urea nitrogen, or hyperkalemia, particularly in the presence of insulin-requiring diabetes mellitus. Serum creatinine levels often underestimate renal dysfunction, particularly in the elderly, in whom estimated creatinine clearance less than 50 mL per min should trigger a reduction of the initial dose of spironolactone to 12.5 mg daily or of eplerenone to 25 mg daily, and aldosterone antagonists should not be given when clearance is less than 30 mL per minute (Table 7). Patients chronically requiring high doses of diuretics without potassium replacement should be evaluated closely, because potassium handling may be impaired.

Table 7. Guidelines for Minimizing the Risk of Hyperkalemia in Patients Treated With Aldosterone Antagonists

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

ACEI indicates angiotensin converting enzyme inhibitor.

*Although the entry criteria for the trials of aldosterone antagonists included creatinine greater than 2.5 mg per dL, the majority of patients had creatinine much lower; in 1 trial (98), 95% of patients had creatinine less than or equal to 1.7 mg per dL.

PRACTICAL USE OF ALDOSTERONE ANTAGONISTS. *Risks of Aldosterone Antagonists.* The major risk of aldosterone antagonists is hyperkalemia due to inhibition of potassium excretion. Renal dysfunction may be aggravated, which further impairs potassium excretion. The positive results of a recent trial led to wider use of spironolactone in HF regimens. The subsequent incidence of hyperkalemia was reported to be as high as 24% in one series (312), in which half of the subjects with hyperkalemia had potassium levels in excess of 6 mEq per liter. Similar results were reported from Norway (245). Although this far exceeded the 2% incidence in the large trial, it is comparable to the 13% observed in the preceding pilot trial with a 25-mg dose and 20% with a 50-mg dose.

The potential impact on the overall HF population is suggested by a population-based analysis in Ontario, Canada of more than 30 000 patients taking ACEIs after a hospitalization for HF. After publication of these trial results in 1999, prescriptions for spironolactone in this geographic area more than tripled, the rate of hospitalization for hyperkalemia increased from 2.4 to 11 patients per thousand, and the associated mortality increased from 0.3 to 2 per thousand (246). These observations lead to a strong recommendation for caution in the selection and monitoring of patients to be given aldosterone antagonists, because the observations make it

clear that clinical trial populations are highly selected, and there is a great increase in evidence of toxicity when the trial results are applied to the general population.

Although aldosterone antagonists usually have a relatively weak diuretic effect, some patients may experience marked potentiation of other diuretic therapy after the addition of aldosterone antagonists. Fluid depletion can occur, which further increases the risk of renal dysfunction and hyperkalemia. During chronic therapy after initial stabilization, hyperkalemia may occur in the setting of other conditions that cause volume depletion, such as gastroenteritis. Gynecomastia or other antiandrogen effects that can occur during therapy with spironolactone are not generally seen with the newer aldosterone antagonist eplerenone (98).

PRACTICAL USE OF ALDOSTERONE ANTAGONISTS. *Initiation and Monitoring.* Spironolactone should be initiated at a dose of 12.5 to 25 mg daily, or occasionally on alternate days. Eplerenone was used after MI in one study (98) at doses of 25 mg per day, increasing to 50 mg daily. Potassium supplementation is generally stopped after the initiation of aldosterone antagonists, and patients should be counseled to avoid high potassium-containing foods. However, patients who have required large amounts of potassium supplementation may need to continue receiving supplementation, albeit at a lower dose, particularly when previous episodes of hypokalemia have been associated with ventricular arrhythmias. On the other hand, potassium supplementation required during vigorous therapy of fluid overload is often no longer necessary once the goal is to maintain even fluid balance. Patients should be cautioned to avoid the addition of nonsteroidal anti-inflammatory agents and cyclo-oxygenase-2 inhibitors, which can lead to worsening renal function and hyperkalemia. Potassium levels and renal function should be rechecked within 3 days and again at 1 week after initiation of an aldosterone antagonist. Subsequent monitoring should be dictated by the general clinical stability of renal function and fluid status but should occur at least monthly for the first 3 months and every 3 months thereafter. The addition or an increase in dosage of ACEIs or ARBs should trigger a new cycle of monitoring. In view of the potential risk for hyperkalemia, the Writing Committee recommends that the routine triple combination of ACEIs, ARBs, and an aldosterone antagonist be avoided.

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

4.3.1.2.3. BETA-ADRENERGIC RECEPTOR BLOCKERS. Beta-blockers act principally to inhibit the adverse effects of the sympathetic nervous system in patients with HF, and these

effects far outweigh their well-known negative inotropic effects. Whereas cardiac adrenergic drive initially supports the performance of the failing heart, long-term activation of the sympathetic nervous system exerts deleterious effects that can be antagonized by the use of beta-blockers. Sympathetic activation can increase ventricular volumes and pressure by causing peripheral vasoconstriction (247) and by impairing sodium excretion by the kidneys (248). 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 (215, 249, 250). 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 (138, 251-253). 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 (254). These deleterious effects are mediated through actions on alpha-1-, beta-1-, and beta-2-adrenergic receptors (138, 215, 247-254).

Three beta-blockers have been shown to be effective in reducing the risk of death in patients with chronic HF: bisoprolol (255) and sustained-release metoprolol (succinate) (256), which selectively block beta-1-receptors, and carvedilol (263, 264), which blocks alpha-1-, beta-1-, and beta-2-receptors. Positive findings with these 3 agents, however, should not be considered indicative of a beta-blocker class effect, as shown by the lack of effectiveness of bucindolol and the lesser effectiveness of short-acting metoprolol in clinical trials (257-259). Patients who have Stage C HF should be treated with 1 of these 3 beta-blockers.

The relative efficacy among these 3 agents is not known, but available evidence does suggest that beta-blockers can differ in their effects on survival (257). In one trial (259), carvedilol (target dose 25 mg twice daily) was compared with immediate-release metoprolol tartrate (target dose 50 mg twice daily). In that trial, carvedilol was associated with a significantly reduced mortality compared with metoprolol tartrate. Although both the dose and the formulation of metoprolol (metoprolol tartrate) used in the above-referenced trial are commonly prescribed by physicians for the treatment of HF, they were neither the dose nor the formulation used in the controlled trial (256) that showed that sustained-release metoprolol (metoprolol succinate) reduces the risk of death (260). There have been no trials to explore whether the survival benefits of carvedilol are greater than those of sustained-released metoprolol when both are used at the target doses.

Effect of Beta-Blockers in the Management of HF. Beta-blockers have now been evaluated in more than 20 000 patients with HF who participated in more than 20 published placebo-controlled clinical trials (72, 76, 255, 260-265). All trials enrolled patients with reduced LVEF (EF less than 35% to 45%) who had already been treated with diuretics and an

ACEI, with or without digitalis. These trials recruited many types of patients, including women and the elderly, as well as patients with a wide range of causes and severity of LV dysfunction, but patients with preserved systolic function, low heart rates (less than 65 beats per min), or low systolic blood pressure (less than 85 mm Hg) and those who were hospitalized or who had class IV HF were not recruited or represented a small proportion of the patients who participated in these published studies. An exception was one trial with carvedilol that enrolled clinically stable patients with NYHA class III and IV symptoms who were free of edema. That trial also demonstrated a reduction in mortality similar to the trials of patients with less advanced disease (263).

This collective experience indicates that long-term treatment with beta-blockers can lessen the symptoms of HF, improve the clinical status of patients, and enhance the patient's overall sense of well-being (266-273). In addition, like ACEIs, beta-blockers can reduce the risk of death and the combined risk of death or hospitalization (255, 260, 262, 263, 274). These benefits of beta-blockers were seen in patients with or without coronary artery disease and in patients with or without diabetes mellitus, as well as in women and black patients. The favorable effects of beta-blockers were also observed in patients already taking ACEIs, which suggests that combined blockade of the 2 neurohormonal systems can produce additive effects.

PRACTICAL USE OF BETA-BLOCKERS. Selection of patients. Beta-blockers should be prescribed to all patients with stable HF due to reduced LVEF unless they have a contraindication to their use or have been shown to be unable to tolerate treatment with these drugs. Because of the favorable effects of beta-blockers on survival and disease progression, treatment with a beta-blocker should be initiated as soon as LV dysfunction is diagnosed. Even when symptoms are mild or have responded to other therapies, beta-blocker therapy is important and should not be delayed until symptoms return or disease progression is documented during treatment with other drugs. Therefore, even if patients do not benefit symptomatically because they have little disability, they should receive treatment with a beta-blocker to reduce the risk of disease progression, future clinical deterioration, and sudden death (255, 260, 262, 273, 274).

Patients need not be taking high doses of ACEIs before being considered for treatment with a beta-blocker, because most patients enrolled in the beta-blocker trials were not taking high doses of ACEIs. Furthermore, in patients taking a low dose of an ACEI, the addition of a beta-blocker produces a greater improvement in symptoms and reduction in the risk of death than an increase in the dose of the ACEI, even to the target doses used in clinical trials (197, 275). In patients with current or recent history of fluid retention, beta-blockers should not be prescribed without diuretics, because diuretics are needed to maintain sodium and fluid balance and prevent the exacerbation of fluid retention that can accompany the initiation of beta-blocker therapy (276-278).

Which patients are sufficiently stable to be considered for treatment with a beta-blocker? Regardless of the severity of

symptoms, patients should not be hospitalized in an intensive care unit, should have no or minimal evidence of fluid overload or volume depletion, and should not have required recent treatment with an intravenous positive inotropic agent. Those excluded from treatment for these reasons should first receive intensified treatment with other drugs for HF (e.g., diuretics) and then be re-evaluated for beta-blockade after clinical stability has been achieved. Beta-blockers may be considered in patients who have reactive airway disease or asymptomatic bradycardia but should be used with great caution or not at all in patients with persistent symptoms of either condition.

PRACTICAL USE OF BETA-BLOCKERS. *Initiation and maintenance.* Treatment with a beta-blocker should be initiated at very low doses (see Table 6), 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 (276-278), 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 (255, 260, 262, 263). Recent data show that beta-blockers can be safely started before discharge even in patients hospitalized for HF, provided they do not require intravenous therapy for HF (279).

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

Once the target dose has been achieved, patients can generally continue long-term therapy with a beta-blocker with little difficulty. Patients should be advised that clinical responses to the drug are generally delayed and may require 2 to 3 months to become apparent (159). 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 (280).

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 (281). However, if the deterioration in clinical status is characterized by hypoperfusion or requires the use of intravenous positive inotropic drugs, it may be prudent to halt or significantly reduce treatment with beta-blockers temporarily until the status of the patient stabilizes. In such patients, positive inotropic agents whose effects are mediated independently of the beta-receptor (e.g., a phosphodiesterase inhibitor such as milrinone) may be preferred. Once stabilized, the beta-blocker should be reintroduced to reduce the subsequent risk of clinical deterioration.

PRACTICAL USE OF BETA-BLOCKERS. *Risks of treatment.* Initiation of treatment with a beta-blocker has produced 4 types of adverse reactions that require attention and management, as discussed below.

1. FLUID RETENTION AND WORSENING HF

Initiation of therapy with a beta-blocker can cause fluid retention (276-278), 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 (282). 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. Reinitiation at a later time or with a different effective beta-blocker may be successful.

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. The role of pacemaker therapy with or without cardiac resynchronization therapy (CRT) to permit the use of beta-blocker therapy is entirely unknown.

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 (262). For beta-blockers that also block alpha-receptors, such as carvedilol, these vasodilatory side effects are generally seen within 24 to 48 hours of the first dose or the first increments in dose and usually subside with repeated dosing without any change in dose. Physicians may minimize the risk of hypotension by administering the beta-blocker and ACEI at different times during the day. If this is ineffective, the occurrence of hypotension may require a temporary reduction in the dose of the ACEI. Hypotensive symptoms may also resolve after a decrease in the dose of diuretics in patients who are volume depleted, but in the absence of such depletion, relaxation of diuretic therapy may increase the risk or consequences of fluid retention (276-278). If hypotension is accompanied by other clinical evidence of hypoperfusion, beta-blocker therapy should be decreased or discontinued pending further patient evaluation.

4.3.1.2.4. 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) (283). 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 (284, 285). In addition, by inhibiting $\text{Na}^+\text{-K}^+$ ATPase in the kidney, digitalis reduces the renal tubular reabsorption of sodium (286); the resulting increase in the delivery of sodium to the distal tubules leads to the suppression of renin secretion from the kidneys (287). 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 (288). 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 (157, 289-294). 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 ACEIs). In a long-term trial that enrolled patients who primarily had class II or III symptoms, treatment with digoxin for 2 to 5 years had no effect on mortality but modestly reduced the combined risk of death and hospitalization (113).

PRACTICAL USE OF DIGITALIS IN HF. *Selection of patients.* Physicians may consider adding digoxin in patients with persistent symptoms of HF during therapy with diuretics, an ACEI (or ARB), and a beta-blocker (295, 296). Digoxin may also be added to the initial regimen in patients with severe symptoms who have not yet responded symptomatically during treatment with diuretics, an ACEI, and beta-blockers. Alternatively, treatment with digoxin may be delayed until the patient's response to ACEIs and beta-blockers has been defined and be used only in patients who remain symptomatic despite therapy with the neurohormonal antagonists. Yet another strategy is to initiate aldosterone antagonists in this type of symptomatic patient and delay the addition of digoxin except in patients who do not respond or who cannot tolerate aldosterone antagonists. If a patient is taking digoxin but not an ACEI or a beta-blocker, treatment with digoxin should not be withdrawn, but appropriate therapy with the neurohormonal antagonists should be instituted. Digoxin is prescribed routinely in patients with HF and chronic atrial fibrillation, but beta-blockers are usually more effective when added to digoxin in controlling the ventricular response, particularly during exercise (297-300). Because beta blockers improve survival and may be effective in controlling rate alone, digoxin should be considered as an adjunctive agent for rate control.

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

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

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

Therapy with digoxin is commonly initiated and maintained at a dose of 0.125 to 0.25 mg daily. Low doses (0.125 mg daily or every other day) should be used initially if the patient is more than 70 years old, has impaired renal function, or has a low lean body mass (301). Higher doses (e.g., digoxin 0.375 to 0.50 mg daily) are rarely used or needed in the management of patients with HF. There is no reason to use loading doses of digoxin to initiate therapy in patients with HF.

Doses of digoxin that achieve a concentration of drug in plasma in the range of 0.5 to 1.0 ng per mL are suggested given the limited evidence currently available. There has been no prospective, randomized evaluation of the relative efficacy or safety of different plasma concentrations of digoxin. Retrospective analysis of 2 studies of digoxin withdrawal found that the prevention of worsening HF by digoxin at lower concentrations in plasma (0.5 to 0.9 ng per mL) was as great as that achieved at higher concentrations (302). In a retrospective analysis of the Digitalis Investigation Group trial, risk-adjusted mortality increased as the plasma concentrations exceeded 1.0 ng per mL (303). However, the likelihood that reduced clearance of digoxin by renal and hepatic P-glycoprotein transporters reflects HF severity provides an alternate explanation of the relationship of higher plasma levels with mortality, and the most conservative interpretation is that levels of digoxin greater than 1.0 ng per mL were not associated with a superior outcome.

PRACTICAL USE OF DIGITALIS IN HF. *Risks of treatment.* When administered with attention to dose and to factors that alter its disposition, digoxin is well tolerated by most patients with HF (304). The principal adverse reactions occur primarily when digoxin is administered in large doses, but large doses may not be needed to produce clinical benefits (305-307). The major side effects include cardiac arrhythmias (e.g., ectopic and re-entrant cardiac rhythms and heart block), gastrointestinal symptoms (e.g., anorexia, nausea, and vomiting), and neurological complaints (e.g., visual disturbances, disorientation, and confusion). Overt digitalis toxicity is commonly associated with serum digoxin levels greater than 2 ng per mL. However, toxicity may occur with lower digoxin levels, especially if hypokalemia, hypomagnesemia, or hypothyroidism coexists (308, 309). The concomitant use of clarithromycin, erythromycin, amiodarone, itraconazole, cyclosporine, verapamil, or quinidine can increase serum digoxin concentrations and may increase the likelihood of digitalis toxicity (310-312). The dose of digoxin should be reduced if treatment with these drugs is initiated. Spironolactone does not inhibit the disposition of digoxin (313); cross-reactivity of some digoxin antibodies with spironolactone confounded earlier attempts to assess the

effect of spironolactone on digoxin clearance. In addition, a low lean body mass and impaired renal function can also elevate serum digoxin levels, which may explain the increased risk of digitalis toxicity in elderly patients. Of note, one analysis suggested that women may not benefit from digoxin therapy and may be at increased risk for death with such therapy (314).

In addition to these established side effects, there is concern that levels of digoxin that previously had been considered to be in the therapeutic range (up to 2 ng per mL) may exert deleterious cardiovascular effects in the long term, even though such levels appear to be well tolerated in the short-term. In one major long-term trial, serum digoxin concentrations in the therapeutic range were associated with an increased frequency of hospitalizations for cardiovascular events other than HF and an increased risk of death due to arrhythmias or MI (113). 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 (315). Digoxin should be used with caution or not used at all in post-MI patients, particularly if they have ongoing ischemia (316).

The Writing Committee has re-evaluated the evidence pertinent to the value of digitalis therapy in patients with HF. Although no new data or trials using digitalis have emerged since publication of the 2001 guidelines, the Writing Committee believes that in terms of safety and efficacy, digitalis does not compare favorably with such agents as the aldosterone blockers, to which the Writing Committee has assigned a Class IIa level of recommendation. If digitalis were a new drug with clinical trials showing a very narrow risk/benefit ratio (especially for potential use in the aging population) and no mortality benefit, it would clearly not be considered for a Class I recommendation. The Writing Committee, therefore, decided to change the level of recommendation for digitalis glycosides from Class I to Class IIa in the current document.

4.3.1.2.5. VENTRICULAR ARRHYTHMIAS AND PREVENTION OF SUDDEN DEATH. Patients with LV dilation and reduced LVEF frequently manifest ventricular tachyarrhythmias, both non-sustained ventricular tachycardia (VT) and sustained VT. The cardiac mortality of patients with all types of ventricular tachyarrhythmias is high. The high mortality results from progressive HF, as well as from sudden death. Sudden death is often equated with a primary arrhythmic event, but multiple causes of sudden death have been documented and include ischemic events such as acute MI (198), electrolyte disturbances, pulmonary or systemic emboli, or other vascular events. Although ventricular tachyarrhythmias are the most common rhythms associated with unexpected sudden death, bradycardia and other pulseless supraventricular rhythms are common in patients with advanced HF (317).

Sudden death can be decreased meaningfully by the therapies that decrease disease progression, as discussed elsewhere in these guidelines. For instance, clinical trials with beta-blockers have shown a reduction in sudden death, as well as in all-cause mortality, in both postinfarction patients and patients with HF regardless of cause (104, 105, 255, 260, 262). Aldosterone antagonists decrease sudden death and overall mortality in HF early after MI and in advanced HF (98). Sudden unexpected death can be decreased further by the use of implanted devices that terminate sustained arrhythmias (318). Even when specific antiarrhythmic therapy is necessary to diminish recurrent ventricular tachyarrhythmias and device firings, the frequency and tolerance of arrhythmias may be improved with appropriate therapy for HF. In some cases, definitive therapy of myocardial ischemia or other reversible factors may prevent recurrence of tachyarrhythmia, particularly polymorphic VT, ventricular fibrillation, and nonsustained VT. Nonetheless, implantable defibrillators would be recommended in all patients who have had a life-threatening tachyarrhythmia and have otherwise good prognosis.

The absolute frequency of sudden death is highest in patients with severe symptoms, or Stage D HF. Many patients with end-stage symptoms experience "sudden death" that is nonetheless expected. Prevention of sudden death in this population could potentially shift the mode of death from sudden to that of progressive HF without decreasing total mortality, as competing risks of death emerge. On the other hand, prevention of sudden death in mild HF may allow many years of meaningful survival. This makes it imperative for physicians to not only assess an individual patient's risk for sudden death but also to assess overall prognosis and functional capacity before consideration of device implantation.

Secondary Prevention of Sudden Death. Patients with previous cardiac arrest or documented sustained ventricular arrhythmias have a high risk of recurrent events. Implantation of an ICD has been shown to reduce mortality in cardiac arrest survivors. An ICD is indicated for secondary prevention of death from ventricular tachyarrhythmias in patients with otherwise good clinical function and prognosis, for whom prolongation of survival is a goal. Patients with chronic HF and a low EF who experience syncope of unclear origin have a high rate of subsequent sudden death and should also be considered for placement of an ICD (319). However, when ventricular tachyarrhythmias occur in a patient with a progressive and irreversible downward spiral of clinical HF decompensation, placement of an ICD is not indicated to prevent recurrence of sudden death, because death is likely imminent regardless of mode. An exception may exist for the small minority of patients for whom definitive therapy such as cardiac transplantation is planned.

Primary Prevention of Sudden Death. Patients with low EF without prior history of cardiac arrest, spontaneous VT, or

inducible VT (positive programmed electrical stimulation study) have a risk of sudden death that is lower than for those who have experienced previous events, but it remains significant. Within this group, it has not yet been possible to identify those patients at highest risk, especially in the absence of prior MI. Approximately 50% to 70% of patients with low EF and symptomatic HF have episodes of nonsustained VT on routine ambulatory electrocardiographic monitoring; however, it is not clear whether the occurrence of complex ventricular arrhythmias in these patients with HF contributes to the high frequency of sudden death or, alternatively, simply reflects the underlying disease process (320-322). Antiarrhythmic drugs to suppress premature ventricular depolarizations and nonsustained ventricular arrhythmias have not improved survival (323, 324), although nonsustained VT may play a role in triggering ventricular tachyarrhythmias. 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 low EF (127, 325, 326). This risk is especially high with the use of Class IA agents (quinidine and procainamide), Class IC agents (flecainide and encainide), and some Class III agents (D-sotalol) (323, 324, 327, 328), which have increased mortality in post-MI trials (329).

Amiodarone is a Class III antiarrhythmic agent but differs from other drugs in this class in having a sympatholytic effect on the heart (330). Amiodarone has been associated with overall neutral effects on survival when given to patients with low EF and HF (331-334). Amiodarone therapy may also act through mechanisms other than antiarrhythmic effects, because amiodarone has been shown in some trials to increase LVEF and decrease the incidence of worsening HF (332, 333). Side effects of amiodarone have included thyroid abnormalities, pulmonary toxicity, hepatotoxicity, neuropathy, insomnia, and numerous other reactions. Therefore, amiodarone should not be considered as part of the routine treatment of patients with HF, with or without frequent premature ventricular depolarizations or asymptomatic nonsustained VT; however, it remains the agent most likely to be safe and effective when antiarrhythmic therapy is necessary to prevent recurrent atrial fibrillation or symptomatic ventricular arrhythmias. Other pharmacological antiarrhythmic therapies, apart from beta-blockers, are rarely indicated in HF but may occasionally be used to suppress recurrent ICD shocks when amiodarone has been ineffective or discontinued owing to toxicity.

The role of ICDs in the primary prevention of sudden death in patients without prior history of symptomatic arrhythmias has been explored recently in a number of trials. If sustained ventricular tachyarrhythmias can be induced in the electrophysiology laboratory in patients with previous MI or chronic ischemic heart disease, the risk of sudden death in these patients is in the range of 5% to 6% per year and can be improved by ICD implantation (335).

The role of ICD implantation for the primary prevention of sudden death in patients with HF and low EF and no history

of spontaneous or inducible VT has been addressed by several large trials that used only readily available clinical data as entry criteria (334, 336, 337). The first of these demonstrated that ICDs, compared with standard medical therapy, decreased the occurrence of total mortality for patients with EF less than or equal to 30% after remote MI (336). Absolute mortality was decreased in the ICD arm by 5.6%, a relative decrease of 31% over 20 months. In a second trial, a survival benefit was not demonstrated with devices implanted within 6 to 40 days after an acute MI in patients who at that time had an EF less than 35% and abnormal heart rate variability. Although sudden deaths were decreased, there was an increase in other events, and ICD implantation did not confer any survival benefit in this setting (337). A third trial examining the benefit of ICD implantation for patients with EF less than 35% and NYHA class II to III symptoms of HF included both ischemic and nonischemic causes of HF; absolute mortality was decreased by 7.2% over a 5-year period in the arm that received a simple "shock-box" ICD with backup pacing at a rate of 40 beats per min. This represented a relative mortality decrease of 23%, which was a survival increase of 11% (334). There was no improvement in survival during the first year, with a 1.8% absolute survival benefit per year averaged over the next 4 years. The Defibrillators in Non-Ischemic Cardiomyopathy Treatment Evaluation (DEFINITE) trial compared medical therapy alone with medical therapy plus an ICD in patients with nonischemic cardiomyopathy, NYHA class I to III HF, and an LVEF less than 36% (338). The ICD was associated with a reduction in all-cause mortality that did not reach statistical significance but was consistent in terms of magnitude of effect (30%) with the findings of the Multicenter Automatic Defibrillator Implantation Trial (MADIT II) (336) and the Sudden Cardiac Death in Heart Failure: Trial of prophylactic amiodarone versus implantable defibrillator therapy (SCD-HeFT) (334). There is an intrinsic variability in measurement of EF particularly shortly after recovery from an acute coronary syndrome event.

ICDs are highly effective in preventing death due to ventricular tachyarrhythmias; however, frequent shocks from an ICD can lead to a reduced quality of life, whether triggered appropriately by life-threatening rhythms or inappropriately by sinus or other supraventricular tachycardia. For symptoms from recurrent discharges triggered by ventricular arrhythmias or atrial fibrillation, antiarrhythmic therapy, most often amiodarone, may be added. For recurrent ICD discharges from VT despite antiarrhythmic therapy, catheter ablation may be effective (339).

It is important to recognize that ICDs have the potential to aggravate HF and have been associated with an increase in HF hospitalizations (336, 340). This may result from right ventricular pacing that produces dyssynchronous cardiac contraction; however, the occurrence of excess nonsudden events with ICDs placed early after MI suggests that other factors may also limit the overall benefit from ICDs. Careful attention to the details of ICD implantation, programming, and pacing function is important for all patients with low EF who are treated with an ICD. The ACC/AHA/NASPE 2002

Guideline Update for Implantation of Cardiac Pacemakers and Antiarrhythmia Devices (341) provides further discussion of the potential problem of worsening HF and LV function in all patients with right ventricular pacing.

The decision regarding the balance of potential risks and benefits of ICD implantation for an individual patient thus remains a complex one. A decrease in incidence of sudden death does not necessarily translate into decreased total mortality, and decreased total mortality does not guarantee a prolongation of survival with meaningful quality of life. This concept is particularly important in patients with limited prognosis owing to advanced HF or other serious comorbidities, because there was no survival benefit observed from ICD implantation until after the first year in 2 of the major trials (334, 336). Furthermore, the average age of patients with HF and low EF is over 70 years, a population not well represented in any of the ICD trials. Comorbidities common in the elderly population, such as prior stroke, chronic pulmonary disease, and crippling arthritic conditions, as well as nursing home residence, should be factored into discussions regarding ICD. Atrial fibrillation, a common trigger for inappropriate shocks, is more prevalent in the elderly population. The gap between community and trial populations is particularly important for a device therapy that may prolong survival but has no positive impact on function or quality of life. Some patients may suffer a diminished quality of life because of device-site complications, such as bleeding, hematoma, or infections, or after ICD discharges, particularly those that are inappropriate.

Consideration of ICD implantation is thus recommended in patients with EF less than 30% and mild to moderate symptoms of HF and in whom survival with good functional capacity is otherwise anticipated to extend beyond 1 year. Because medical therapy may substantially improve EF, consideration of ICD implants should follow documentation of sustained reduction of EF despite a course of beta-blockers and ACEIs or ARBs; however, ICDs are not warranted in patients with refractory symptoms of HF (Stage D) or in patients with concomitant diseases that would shorten their life expectancy independent of HF. The appropriate management of patients with HF and an EF between 30% and 35% remains controversial. Risk may be further stratified for patients with coronary artery disease by performing a programmed electrical stimulation study to demonstrate inducible VT. In the patient with idiopathic cardiomyopathy and an EF of 30% to 35%, the physician might want to continue intensive medical therapy with those drugs shown to improve EF and delay disease progression before giving consideration to ICD implantation.

Before implantation, patients should be fully informed of their cardiac prognosis, including the risk of both sudden and nonsudden mortality; the efficacy, safety, and risks of an ICD; and the morbidity associated with an ICD shock. Patients and families should clearly understand that the ICD does not improve clinical function or delay HF progression. Most importantly, the possible reasons and process for potential future deactivation of defibrillator features should be dis-

cussed long before functional capacity or outlook for survival is severely reduced.

4.3.1.3. Interventions to Be Considered for Use in Selected Patients

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

4.3.1.3.1. ISOSORBIDE DINITRATE. Isosorbide dinitrate was one of the first vasodilator agents reported to be useful for chronic therapy of HF. Nitrate therapy may decrease symptoms of dyspnea at night and during exercise and may improve exercise tolerance in patients who have persistent limitations despite optimization of other therapies (342). Most experience relates to the oral dinitrate and more recently the mononitrate preparations, with little information available about topical nitrate therapy in this population. Recent evidence suggests that nitrates can inhibit abnormal myocardial and vascular growth (343, 344) and may thereby attenuate the process of ventricular remodeling (345) and improve symptoms.

The only common side effects of nitrate therapy are headaches and hypotension. In clinical use, nitrates are frequently prescribed to patients with persistent congestive symptoms. Although the only large trial of nitrates in HF (355) used a combination of nitrates and hydralazine, nitrates predominantly are potent venodilators that also have effects on arterial tone when used alone, particularly when systemic vascular resistance is severely elevated. Because they act through cyclic guanosine monophosphate, there is a theoretical reason that they may be titrated up to facilitate weaning of intravenous infusions that act through the same pathway.

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

4.3.1.3.2. HYDRALAZINE. Hydralazine is an arterial vasodilator with relatively little effect on venous tone and cardiac filling pressures. The rationale for its combined use with nitrates was to achieve both venous and arterial vasodilation (346, 347). In addition to its direct vascular actions, hydralazine in theory may interfere with the biochemical and molecular mechanisms responsible for the progression of HF (348, 349) and the development of nitrate tolerance (350-353). There are limited data regarding the use of hydralazine alone in HF.

4.3.1.3.3. HYDRALAZINE AND ISOSORBIDE DINITRATE. In a large-scale trial that compared the vasodilator combination with placebo, the use of hydralazine and isosorbide dinitrate reduced mortality but not hospitalizations in patients with HF treated with digoxin and diuretics but not an ACEI or

beta-blocker (354, 355). However, in another large-scale trial that compared the vasodilator combination with an ACEI, the ACEI produced more favorable effects on survival (194), a benefit not evident in the subgroup of patients with class III to IV HF. In both trials, the use of hydralazine and isosorbide dinitrate produced frequent adverse reactions (primarily headache and gastrointestinal complaints), and many patients could not continue treatment at target doses.

Of note, a post hoc retrospective analysis of both vasodilator trials demonstrated particular efficacy of isosorbide dinitrate and hydralazine in the black cohort (528). A confirmatory trial has been done. In that trial, which was limited to the black population with HF, the addition of hydralazine and isosorbide dinitrate to standard therapy with an ACEI and/or a beta-blocker was shown to be of significant benefit (356). The benefit was presumed to be related to enhanced nitric oxide bioavailability. Whether this benefit is evident in other patients with HF remains to be investigated. The combination of hydralazine and isosorbide dinitrate should not be used for the treatment of HF in patients who have no prior use of an ACEI and should not be substituted for ACEIs in patients who are tolerating ACEIs without difficulty.

Despite the lack of data with the vasodilator combination in patients who are intolerant of ACEIs, the combined use of hydralazine and isosorbide dinitrate may be considered as a therapeutic option in such patients. However, compliance with this combination has generally been poor because of the large number of tablets required and the high incidence of adverse reactions (194, 354). For patients with more severe symptoms and ACEI intolerance, the combination of hydralazine and nitrates is used frequently, particularly when ACEI therapy is limited by hypotension or renal insufficiency. There are, however, no trials addressing the use of isosorbide dinitrate and hydralazine specifically in the population of patients who have persistent symptoms and intolerance to inhibitors of the renin-angiotensin system.

4.3.1.3.4. CARDIAC RESYNCHRONIZATION THERAPY. Approximately one third of patients with low EF and class III to IV symptoms of HF manifest a QRS duration greater than 120 ms (357-359). This electrocardiographic representation of abnormal cardiac conduction has been used to identify patients with dyssynchronous ventricular contraction. While imperfect, no other consensus definition of cardiac dyssynchrony exists as yet, although several echocardiographic measures appear promising. The mechanical consequences of dyssynchrony include suboptimal ventricular filling, a reduction in LV dp/dt (rate of rise of ventricular contractile force or pressure), prolonged duration (and therefore greater severity) of mitral regurgitation, and paradoxical septal wall motion (360-362). Ventricular dyssynchrony has also been associated with increased mortality in HF patients (363-365). Dyssynchronous contraction can be addressed by electrically activating the right and left ventricles in a synchronized manner with a biventricular pacemaker device. This approach to HF therapy, commonly called cardiac resynchronization therapy (CRT), may enhance ventricular con-

traction and reduce the degree of secondary mitral regurgitation (366-368). In addition, the short-term use of CRT has been associated with improvements in cardiac function and hemodynamics without an accompanying increase in oxygen utilization (369), as well as adaptive changes in the biochemistry of the failing heart (367).

To date, more than 4,000 HF patients with ventricular dyssynchrony have been evaluated in randomized controlled trials of optimal medical therapy alone versus optimal medical therapy plus CRT with or without an ICD. Cardiac resynchronization therapy, when added to optimal medical therapy in persistently symptomatic patients, has resulted in significant improvements in quality of life, functional class, exercise capacity (by peak oxygen uptake) and exercise distance during a 6-minute walk test, and EF in patients randomized to CRT (370) or to the combination of CRT and ICD (318, 371, 372). In a meta-analysis of several CRT trials, HF hospitalizations were reduced by 32% and all-cause mortality by 25%. The effect on mortality in this meta-analysis became apparent after approximately 3 months of therapy (372). In one study, subjects were randomized to optimal pharmacological therapy alone, optimal medical therapy plus CRT alone, or optimal medical therapy plus the combination of CRT and an ICD. Compared with optimal medical therapy alone, both device arms significantly decreased the combined risk of all-cause hospitalization and all-cause mortality by approximately 20%, whereas the combination of a CRT and an ICD decreased all-cause mortality significantly by 36% (373). More recently, in a randomized controlled trial comparing optimal medical therapy alone with optimal medical therapy plus CRT alone (without a defibrillator), CRT significantly reduced the combined risk of death of any cause or unplanned hospital admission for a major cardiovascular event (analyzed as time to first event) by 37% (374). In that trial, all-cause mortality was significantly reduced by 36% and HF hospitalizations by 52% with the addition of CRT. Thus, there is strong evidence to support the use of CRT to improve symptoms, exercise capacity, quality of life, LVEF, and survival and to decrease hospitalizations in patients with persistently symptomatic HF undergoing optimal medical therapy who have cardiac dyssynchrony (as evidenced by a prolonged QRS duration). The use of an ICD in combination with CRT should be based on the indications for ICD therapy.

With few exceptions, resynchronization trials have enrolled patients in normal sinus rhythm. Although the entry criteria specified QRS duration only over 120 ms, the average QRS duration in the large trials was more than 150 ms, with less information demonstrating benefit in patients with lesser prolongation of QRS. Two small studies, one randomized (375) and the other observational (376), evaluated the potential benefit of CRT in HF patients with ventricular dyssynchrony and atrial fibrillation. Although both studies demonstrated the benefit of CRT in these patients, the total number of patients examined (fewer than 100) precludes a recommendation for CRT in otherwise eligible patients with atrial fibrillation. To date, only a small number of patients with "pure" right bundle-branch block have been enrolled in CRT trials. The effect of CRT in these patients is currently

unknown. Similarly, the prolonged QRS duration associated with right ventricular pacing has also been associated with ventricular dyssynchrony that may be improved by CRT, but no studies have addressed this situation as yet. Recommendations regarding CRT for patients with right bundle-branch block, atrial fibrillation, minor conduction abnormality, and pacemaker dependence as well as inadequate medical therapy must await the completion of ongoing or future trials.

Ten studies have reported on CRT peri-implant morbidity and mortality. There were 13 deaths in 3,113 patients (0.4%). From a pooled assessment of 3,475 patients in 17 studies, the success rate of implantation was approximately 90% (372). Device-related problems during the first 6 months after implantation reported in 13 studies included lead malfunction or dislodgement in 8.5%, pacemaker problems in 6.7%, and infection in 1.4% of cases. These morbidity and mortality data are derived from trials that used expert centers. Results in individual clinical centers may vary considerably and are subject to a significant learning curve for each center; however, as implantation techniques evolve and equipment improves, complication rates may also decline (372).

4.3.1.3.5. EXERCISE TRAINING. In the past, patients with HF were advised to avoid physical exertion in the hope that bed rest might minimize symptoms (377) and in the belief that physical activity might accelerate the progression of LV dysfunction (378-380); 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 (123, 126). Limitations of activity not only may impair exercise capacity but also may produce adverse psychological effects and impair peripheral vasodilatory responses (125, 381). These findings have led to the hypothesis that exercise training might improve the clinical status of patients with chronic HF (123, 382).

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 (383, 383-392). The improvement was comparable to that achieved with pharmacological interventions (382), was in addition to the benefits of ACEIs and beta-blockers, (384, 385), and was associated with an enhancement of endothelium-dependent peripheral vasodilation and skeletal muscle metabolism (384, 393). 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 minutes 3 to 5 times per week for periods of 8 to 12 weeks (391).

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 (386, 394, 395). In the experimental setting, exercise appears to attenuate the rate of progression of HF (396, 397). These observations suggest that exercise

training might have a favorable effect on the natural history of HF. Only 1 study has evaluated the long-term effect of physical conditioning in patients with HF (392), and in that 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.

4.3.1.4. Drugs and Interventions Under Active Investigation

Several drugs and other interventions are undergoing 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. Several drugs that showed promise in pilot studies and were included in this section in the 2001 guidelines failed to live up to their promise in long-term, large-scale trials and are no longer included as "promising" in this update. Several remain under or have begun active investigation. Investigational drug therapies currently in phase III evaluation for the treatment of chronic HF include vasopressin receptor antagonists, intermittent nesiritide infusions, and oral phosphodiesterase III inhibitors. In addition, newer devices and technologies, such as implantable hemodynamic monitors and internal cardiac support devices, external counterpulsation, treatment for sleep-disordered breathing, myocardial growth factors and stem cell transplantation, and devices to achieve intravascular volume reduction, as well as novel surgical approaches, including surgical ventricular restoration, are under active investigation. Several of these are discussed below.

4.3.1.4.1. TECHNIQUES FOR RESPIRATORY SUPPORT. Patients with HF frequently exhibit abnormal respiratory patterns, including Cheyne-Stokes breathing and sleep-disordered breathing (398). In the Sleep Heart Health Study, the presence of sleep-disturbed breathing was associated with a 2.38 relative risk of HF independent of other known risk factors (399). This risk of HF exceeded that for all other cardiovascular disease syndromes evaluated, including hypertension, stroke, and coronary artery disease. The use of nocturnal oxygen and devices that provide continuous positive airway pressure has been reported to produce symptomatic improvement (400, 401). Although there is no direct evidence that treatment of sleep-disturbed breathing prevents incident HF, treatment of established LV dysfunction with continuous positive airway pressure breathing has been shown to improve LV structure and function in patients with either

obstructive or central sleep apnea disturbed-breathing syndrome (402). 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 identify patients most likely to benefit from treatment.

4.3.1.4.2. EXTERNAL COUNTERPULSATION. The technique of external counterpulsation involves the use of a device with inflatable cuffs that surround the lower limbs and inflate and deflate in synchronization with the cardiac cycle. The device is designed to reduce loading conditions in systole while increasing coronary perfusion pressures in diastole (403). External counterpulsation has been shown to reduce the frequency and severity of anginal attacks in patients with symptomatic coronary artery disease (404). A possible mechanism of action for this observed clinical effect may be an improvement in endothelial function of the coronary vascular bed (405, 406). Early trials of this therapy in patients with HF and low EF have been encouraging, and a randomized trial has been completed recently (407, 408). Until more data are available, routine use of this therapy cannot be recommended for the management of patients with symptomatic reduced LVEF.

4.3.1.4.3. VASOPRESSIN RECEPTOR ANTAGONISTS. Arginine vasopressin is a peptide hormone with significant cardiovascular and renal effects. These effects are mediated through at least 2 receptor subtypes: the V_{1A} receptor, which is found on vascular smooth muscle cells and in the myocardium, and the V_2 receptors, which are found in the kidney. Vasopressin levels are often elevated in patients with HF and LV dysfunction, and they appear to be associated with adverse outcomes in the setting of low EF after MI (409).

Early studies with 2 different vasopressin receptor antagonists have shown favorable changes in hemodynamics and urine output without a significant change in blood pressure or heart rate. The drugs appear to reduce body weight and edema, and they normalized serum sodium in patients with hyponatremia, but the duration and significance of these clinical effects are not clear (410, 411). Currently, longer-term clinical trials are under way to determine the role, if any, of these vasopressin antagonists in patients with chronic HF (412, 413).

4.3.1.4.4. IMPLANTABLE HEMODYNAMIC MONITORS. Several implantable systems are in development for the chronic, remote, outpatient monitoring of ventricular filling pressures and other hemodynamic and clinical variables in HF patients. One such system has completed phase I and II study and is currently being evaluated in a phase III randomized outcomes trial. The hypothesis underlying this approach suggests that changes in therapy to optimize LV filling pressure may improve outcomes in HF patients (414, 415).

4.3.1.4.5. CARDIAC SUPPORT DEVICES. There is developing experience with surgical devices that are designed to alter

physical stresses on the LV; theoretically, the devices may improve performance or attenuate further ventricular dilatation. One such device now being evaluated clinically is a cardiac wrapping device made from a bidirectional woven polyester that allows for shortening but resists circumferential expansion beyond the limits of the wrap (416). Clinical trials in Europe (417) and the United States are currently under way to evaluate the safety and efficacy of this device in patients. Other ventricular constraint or support devices are also under investigation in Europe and the United States.

4.3.1.4.6. SURGICAL APPROACHES UNDER INVESTIGATION. A number of surgical approaches have emerged as potentially beneficial in patients with ischemic HF. The goals of such procedures generally include revascularization, reduction in “geometric” or functional mitral regurgitation, and restoration of a more normal LV geometry and function. In this context, the so-called surgical ventricular restoration procedure is one of the most extensively studied and applied techniques for reshaping or excluding anteroapical and septal regions of asynergy (418-420). The surgical ventricular restoration procedure, although extensively applied to the treatment of LV asynergy, is now being studied prospectively in a randomized trial comparing standard medical therapy versus surgical therapy (coronary artery bypass grafting) alone versus surgical ventricular restoration plus coronary artery bypass grafting in patients with ischemic HF. The National Heart, Lung, and Blood Institute’s multicenter, international, randomized STICH (Surgical Treatment for Ischemic Heart Failure) trial began enrolling patients with coronary artery disease and HF in the Spring of 2002. The goal of this study is to determine whether a benefit over medical therapy can be found for coronary revascularization and whether this benefit can be enhanced by ventricular restoration surgery.

4.3.1.4.7. NESIRITIDE. Natriuretic peptides are novel compounds that promote diuresis and natriuresis, have vasodilatory properties, lead to an indirect increase in cardiac output, and suppress neurohormonal activation; they have been approved for use in the management of acute HF (421-423). In this setting, nesiritide has been shown to improve symptoms of acute HF, but the effect on morbidity and mortality has not been clear from available clinical trials (423a-423b).

They are currently under investigation as adjunctive therapy, administered on an intermittent outpatient basis, for advanced HF. Unless a definitive study does demonstrate safety and efficacy, intermittent or continuous outpatient infusion of nesiritide and other natriuretic peptides is not recommended.

4.3.1.5. Drugs and Interventions of Unproved Value and Not Recommended

4.3.1.5.1. NUTRITIONAL SUPPLEMENTS AND HORMONAL THERAPIES. Patients with HF, particularly those treated with diuretics, may become deficient in vitamins and micronutrients. Several nutritional supplements (e.g., coenzyme Q10, carnitine, taurine, and antioxidants) and hormonal therapies

(e.g., growth hormone or thyroid hormone) have been proposed for the treatment of HF (424-429). Aside from replenishment of documented deficiencies, randomized trials have failed to demonstrate benefit for routine vitamin, nutritional, or hormonal supplementation (430).

In most data or other literature regarding nutraceuticals, there are issues, including outcomes analyses, adverse effects, and drug-nutraceutical interactions, that remain unresolved. No clinical trials have demonstrated improved survival in users of nutritional or hormonal therapy. Some studies have suggested a possible effect for coenzyme Q10 in reduced hospitalization rates, dyspnea, and edema in patients with HF, but these benefits have not been seen uniformly (431-434). Because of possible adverse effects and drug interactions of nutritional supplements and their widespread use, physicians caring for patients with HF should routinely inquire about their use. Until more data are available, nutritional supplements or hormonal therapies are not recommended for the treatment of HF. The ACCF Clinical Expert Consensus Document on the Integration of Complementary Medicine Into Cardiovascular Medicine (in press) will provide more details regarding cardiovascular issues with alternative and complementary medicine.

4.3.1.5.2. INTERMITTENT INTRAVENOUS POSITIVE INOTROPIC THERAPY. Although positive inotropic agents can improve cardiac performance during short- and long-term therapy (435, 436), long-term oral therapy with these drugs has not improved symptoms or clinical status (292, 437-447) and has been associated with a significant increase in mortality, especially in patients with advanced HF (445, 448-453). 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 (41-43, 454).

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 (41-43, 454). 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 (455), 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.

4.3.2. Patients With HF and Normal LVEF

RECOMMENDATIONS

Class I

1. **Physicians should control systolic and diastolic hypertension in patients with HF and normal LVEF, in accordance with published guidelines. (Level of Evidence: A)**
2. **Physicians should control ventricular rate in patients with HF and normal LVEF and atrial fibrillation. (Level of Evidence: C)**
3. **Physicians should use diuretics to control pulmonary congestion and peripheral edema in patients with HF and normal LVEF. (Level of Evidence: C)**

Class IIa

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

Class IIb

1. **Restoration and maintenance of sinus rhythm in patients with atrial fibrillation and HF and normal**

LVEF might be useful to improve symptoms. (Level of Evidence: C)

2. **The use of beta-adrenergic blocking agents, ACEIs, ARBs, or calcium antagonists in patients with HF and normal LVEF and controlled hypertension might be effective to minimize symptoms of HF. (Level of Evidence: C)**
3. **The usefulness of digitalis to minimize symptoms of HF in patients with HF and normal LVEF is not well established. (Level of Evidence: C)**

Table 8 summarizes the recommendations for treatment of patients with HF and normal LVEF.

4.3.2.1. Identification of Patients

For many years, the syndrome of HF was considered to be synonymous with diminished contractility of the LV, or reduced LVEF. Over the past few years, however, there has been a growing appreciation that a large number of patients with HF have a relatively normal EF, or preserved EF. The pathophysiology of this type of HF has been reviewed in depth (456), and a large, randomized study that enrolled patients with HF and normal EF has been completed (235). Currently, a number of investigators are seeking to clarify the epidemiology, clinical characteristics, and prognosis of patients with HF and a normal LVEF (457).

Depending on the criteria used to delineate HF and the accepted threshold for defining preserved LVEF, it is estimated that as many as 20% to 60% of patients with HF have a relatively (or near) normal LVEF and, in the absence of valvular disease, are believed to have reduced ventricular compliance as a major contributor to the clinical syndrome (458-462). Some investigators have found that in a signifi-

Table 8. Recommendations for Treatment of Patients With Heart Failure and Normal Left Ventricular Ejection Fraction

Recommendation	Class	Level of Evidence
Physicians should control systolic and diastolic hypertension, in accordance with published guidelines.	I	A
Physicians should control ventricular rate in patients with atrial fibrillation.	I	C
Physicians should use diuretics to control pulmonary congestion and peripheral edema.	I	C
Coronary revascularization is reasonable in patients with coronary artery disease in whom symptomatic or demonstrable myocardial ischemia is judged to be having an adverse effect on cardiac function.	IIa	C
Restoration and maintenance of sinus rhythm in patients with atrial fibrillation might be useful to improve symptoms.	IIb	C
The use of beta-adrenergic blocking agents, angiotensin converting enzyme inhibitors, angiotensin II receptor blockers, or calcium antagonists in patients with controlled hypertension might be effective to minimize symptoms of heart failure.	IIb	C
The use of digitalis to minimize symptoms of heart failure is not well established.	IIb	C

cant number of patients, a tendency to fluid retention and reduced vascular compliance, rather than myocardial stiffness, represent the principal abnormalities (463). Regardless, abnormal renal sodium handling and arterial stiffness, in addition to myocardial stiffness, are likely to play important pathophysiologic roles in many patients. Diastole is that period in the cardiac cycle during which the myocardium loses its ability to generate force and shorten and returns to an unstressed length and force, and diastolic dysfunction occurs when these events are prolonged, slowed, or are incomplete (456). It should also be recognized that diastolic function is abnormal in patients with HF and reduced LVEF, as well as those with preserved LVEF. Several recognized myocardial disorders are associated with HF and a normal LVEF, including restrictive cardiomyopathy, obstructive and nonobstructive hypertrophic cardiomyopathy, and infiltrative cardiomyopathies. The vast majority of patients with HF and relatively preserved LVEF have a history of hypertension, and many, if not most, of these patients have evidence of LVH on echocardiography. However, some patients who present with HF and relatively preserved LVEF have no identifiable myocardial pathology. Because these patients usually present with symptoms typical of HF, they should be classified as Stage C. Indeed, most patients will have some detectable structural abnormality of the heart, including LVH, atrial dilation, mitral annular calcification, aortic sclerosis, or myocardial scar.

Heart failure associated with relatively preserved LVEF is most prevalent among elderly women, most of whom have hypertension, diabetes mellitus, or both and often coronary artery disease or atrial fibrillation as well (459). This observation may be related to the fact that aging has a greater impact on ventricular filling characteristics than on EF (464). Aging is associated with decreases in the elastic properties of the heart and great vessels, which leads to an increase in systolic blood pressure and an increase in myocardial stiffness. The rate of ventricular filling decreases in part because of structural changes in the heart (due to fibrosis) and because of a decline in relaxation and compliance. These deleterious effects on diastolic function are exacerbated by a decrease in beta-adrenergic receptor density and a decline in peripheral vasodilator capacity, both of which are characteristic of elderly patients. In addition, elderly patients commonly have associated disorders (e.g., coronary artery disease, diabetes mellitus, aortic stenosis, atrial fibrillation, or obesity), which can adversely affect the diastolic properties of the heart or decrease the time available for ventricular filling. There may also be sex-specific responses to hypertension and diabetes mellitus that make women more susceptible than men to the cumulative effects of aging on diastolic function (465).

A number of recent investigations have focused on the differences between HF with preserved EF and that with low LVEF (27, 28, 457). Myocardial infarction or other evidence of atherosclerotic disease appears to be less common in HF with normal LVEF, but hypertension is at least as common in this subgroup. The morbidity and mortality associated with HF and a relatively preserved LVEF may be nearly as pro-

found as that with low LVEF; frequent and repeated hospitalizations characterize the patient with HF and a normal LVEF (466, 467). Most, but not all, series of patients with HF and relatively preserved LVEF have shown better survival than is seen in patients with HF and reduced LVEF; however, these comparisons are difficult to interpret, because it is difficult to be certain that such series do not contain at least some patients in whom the diagnosis of HF is erroneous.

4.3.2.2. Diagnosis

There have been several proposed criteria by which clinicians and investigators may define HF with a relatively preserved LVEF (468-471). In general, a definitive diagnosis can be made when the rate of ventricular relaxation is slowed; this physiological abnormality is characteristically associated with the finding of an elevated LV filling pressure in a patient with normal LV volumes and contractility. In practice, the diagnosis is generally based on the finding of typical symptoms and signs of HF in a patient who is shown to have a normal LVEF and no valvular abnormalities (aortic stenosis or mitral regurgitation, for example) on echocardiography. Every effort should be made to exclude other possible explanations or disorders that may present in a similar manner (462, 473) (Table 9).

Noninvasive methods (especially those that rely on Doppler echocardiography) have been developed to assist in the diagnosis of HF with normal LVEF, but these tests have significant limitations, because cardiac filling patterns are readily altered by nonspecific and transient changes in loading conditions in the heart and by aging, changes in heart rate, or the presence of mitral regurgitation (474-480). The analysis of BNP levels in association with echocardiographic filling patterns can improve diagnostic accuracy, e.g., a normal BNP level along with completely normal diastolic filling parameters makes HF much less likely; however, HF does remain a strictly clinical diagnosis (481).

Table 9. Differential Diagnosis in a Patient With Heart Failure and Normal Left Ventricular Ejection Fraction

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

HF indicates heart failure; LV, left ventricular; and LVEF, left ventricular ejection fraction.

4.3.2.3. Principles of Treatment

In contrast to the treatment of HF due to reduced LVEF, few clinical trials are available to guide the management of patients with HF and relatively preserved LVEF. Although controlled studies have been performed with digitalis, ACEIs, ARBs, beta-blockers, and calcium channel blockers in patients with HF who had a relatively preserved LVEF, for the most part, these trials have been small or have produced inconclusive results (113, 482-485). Nevertheless, many patients with HF and normal LVEF are treated with these drugs because of the presence of comorbid conditions (i.e., atrial fibrillation, hypertension, diabetes mellitus, and coronary artery disease). A large, randomized trial recently completed included patients with HF and normal LVEF, which demonstrates that studies in such patients can be accomplished (235). In that trial, the addition of candesartan to the treatment regimen for patients with symptomatic HF and relatively preserved LVEF significantly reduced morbidity but did not reach the primary end point.

In the absence of other controlled clinical trials, the management of these patients is based on the control of physiological factors (blood pressure, heart rate, blood volume, and myocardial ischemia) that are known to exert important effects on ventricular relaxation (462). Likewise, diseases that are known to cause HF with normal LVEF should be treated, such as coronary artery disease, hypertension, or aortic stenosis. Clinically, it seems reasonable to target symptom reduction, principally by reducing cardiac filling pressures at rest and during exertion (456). Recommendations regarding the use of anticoagulation and antiarrhythmic agents apply to all patients with HF, irrespective of LVEF.

POTENTIAL TREATMENT STRATEGIES. Hypertension exerts a deleterious effect on ventricular function by causing both structural and functional changes in the heart. Increases in systolic blood pressure have been shown to slow myocardial relaxation (486), 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 (61). Consideration should at least be given to achieving target levels of blood pressure lower than those recommended for patients with uncomplicated hypertension (e.g., less than 130 mm Hg systolic and less than 80 mm Hg diastolic) (61, 485, 487). Because myocardial ischemia can impair ventricular relaxation, coronary revascularization should be considered in patients with coronary artery disease in whom symptomatic or demonstrable myocardial ischemia is believed to be exerting a deleterious effect on cardiac function [for more information, see the ACC/AHA 2004 Guideline Update for Coronary Artery Bypass Graft Surgery (29)].

Because tachycardia can shorten the time available for ventricular filling and coronary perfusion, drugs that slow the heart rate or the ventricular response to atrial arrhythmias (e.g., beta-blockers, digoxin, and some calcium channel

blockers) can provide symptomatic relief in patients with HF and normal LVEF. Similarly, patients with HF and preserved LVEF may be particularly sensitive to loss of atrial kick, which supports a potential benefit for restoration of sinus rhythm in patients with atrial fibrillation. The benefits of restoring sinus rhythm in these individuals are less clear, and the large trials of rhythm versus rate control in atrial fibrillation published recently have excluded patients with HF. Moreover, the presence of systolic or diastolic dysfunction may diminish the efficacy and enhance the toxicity of drugs used to achieve and maintain sinus rhythm.

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

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

RECOMMENDATIONS

Class I

1. Meticulous identification and control of fluid retention is recommended in patients with refractory end-stage HF. (*Level of Evidence: B*)
2. Referral for cardiac transplantation in potentially eligible patients is recommended for patients with refractory end-stage HF. (*Level of Evidence: B*)
3. Referral of patients with refractory end-stage HF to an HF program with expertise in the management of refractory HF is useful. (*Level of Evidence: A*)
4. Options for end-of-life care should be discussed with the patient and family when severe symptoms in patients with refractory end-stage HF persist despite application of all recommended therapies. (*Level of Evidence: C*)
5. Patients with refractory end-stage HF and implantable defibrillators should receive information about the option to inactivate defibrillation. (*Level of Evidence: C*)

Class IIa

Consideration of an LV assist device as permanent or "destination" therapy is reasonable in highly selected patients with refractory end-stage HF and an estimated 1-year mortality over 50% with medical therapy. (*Level of Evidence: B*)

Class IIb

1. Pulmonary artery catheter placement may be reasonable to guide therapy in patients with refractory end-stage HF and persistently severe symptoms. (*Level of Evidence: C*)

2. **The effectiveness of mitral valve repair or replacement is not established for severe secondary mitral regurgitation in refractory end-stage HF. (Level of Evidence: C)**
3. **Continuous intravenous infusion of a positive inotropic agent may be considered for palliation of symptoms in patients with refractory end-stage HF. (Level of Evidence: C)**

Class III

1. **Partial left ventriculectomy is not recommended in patients with nonischemic cardiomyopathy and refractory end-stage HF. (Level of Evidence: C)**
2. **Routine intermittent infusions of positive inotropic agents are not recommended for patients with refractory end-stage HF. (Level of Evidence: B)**

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

Before a patient is considered to have refractory HF, physicians should confirm the accuracy of the diagnosis, identify any contributing conditions, and ensure that all conventional medical strategies have been optimally employed. Measures listed as Class I recommendations for patients in stages A, B, and C are also appropriate for patients in end-stage HF (also see Section 5). When no further therapies are appropriate, careful discussion of the prognosis and options for end-of-life care should be initiated (see Section 7).

4.4.1. 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 (148, 161). 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) (169, 171). If the patient continues to exhibit evidence of volume overload despite these measures, hospitalization is generally required for further adjustment of therapy (168, 488), possibly including intravenous dopamine or dobutamine. This strategy can elicit a marked increase in urine volume, but such a diuresis is frequently accompanied by worsening azotemia, especially if patients are also being treated with an ACEI. Provided that renal function stabilizes, small or moderate elevations of blood urea nitrogen and serum creatinine should not lead to efforts to minimize the intensity of therapy; however, if the degree of renal dysfunction is severe or if the edema becomes resistant to treatment, ultrafiltration or hemofiltration may be needed to achieve adequate control of fluid retention (489, 490). 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 (491), because unresolved edema may itself attenuate the response to diuretics (164-166). Once euvolemia is achieved, the patient's dry weight can be defined and used as a continuing target for the adjustment of diuretic doses. Many patients are able to modify their own diuretic regimen in response to changes in weight that exceed a predefined range. The restriction of dietary sodium (to 2 g daily or less) can greatly assist in the maintenance of volume balance. Patients with persistent or recurrent fluid retention despite sodium restriction and high-dose diuretic use may benefit from review of fluid intake and restriction to 2 liters daily. The ongoing control of fluid retention may be enhanced by enrollment in an HF program, which can provide the close surveillance and education needed for the early recognition and treatment of volume overload (143-146).

4.4.2. Utilization of Neurohormonal Inhibitors

Controlled trials suggest that patients with advanced HF respond favorably to treatment with both ACEIs and beta-blockers in a manner similar to those with mild to moderate disease (195-197, 199-201, 204, 209-220, 247-255, 260-263, 492). However, because neurohormonal mechanisms play an important role in the support of circulatory homeostasis as HF progresses, neurohormonal antagonism may be less well tolerated by patients with severe symptoms than by patients with mild symptoms. Patients who are at the end stage of their disease are at particular risk of developing hypotension and renal insufficiency after the administration of an ACEI and of experiencing worsening HF after treatment with a beta-blocker. As a result, patients with refractory HF may tolerate only small doses of these neurohormonal antagonists or may not tolerate them at all.

Consequently, physicians should exercise great care when considering the use of both ACEIs and beta-blockers in

patients with refractory HF. Treatment with either type of drug should not be initiated in patients who have systolic blood pressures less than 80 mm Hg or who have signs of peripheral hypoperfusion. In addition, patients should not be started on a beta-blocker if they have significant fluid retention or if they recently required treatment with an intravenous positive inotropic agent. Treatment with an ACEI or beta-blocker should be initiated in very low doses, and patients should be monitored closely for signs or symptoms of intolerance. If low doses are tolerated, further dosage increments may be considered but may not be tolerated. However, clinical trials with lisinopril and carvedilol suggest that even low doses of these drugs may provide important benefits (272, 493).

Alternative pharmacological treatments may be considered for patients who cannot tolerate ACEIs or beta-blockers. A combination of nitrates and hydralazine has been reported to have favorable effects on survival in patients with mild to moderate symptoms who were not taking an ACEI or a beta-blocker (354), but the utility of this vasodilator combination in patients with end-stage disease who are being given these neurohormonal antagonists remains unknown. In addition, many patients experience headaches or gastrointestinal distress with these direct-acting vasodilators, which can prevent patients from undergoing long-term treatment. Spironolactone has been reported to prolong life and reduce the risk of hospitalization for HF in patients with advanced disease (141); however, the evidence supporting the use of the drug has been derived in patients who have preserved renal function, and the drug can produce dangerous hyperkalemia in patients with impaired renal function. Finally, although ARBs (224) are frequently considered as alternatives to ACEIs because of the low incidence of cough and angioedema with these medications, it is not clear that ARBs are as effective as ACEIs, and they are as likely as ACEIs to produce hypotension or renal insufficiency (196, 494).

4.4.3. Intravenous Peripheral Vasodilators and Positive Inotropic Agents

Patients with refractory HF are hospitalized frequently for clinical deterioration, and during such admissions, they commonly receive infusions of both positive inotropic agents (dobutamine, dopamine, or milrinone) and vasodilator drugs (nitroglycerin, nitroprusside, or nesiritide) in an effort to improve cardiac performance, facilitate diuresis, and promote clinical stability. Some physicians have advocated the placement of pulmonary artery catheters in patients with refractory HF, with the goal of obtaining hemodynamic measurements that might be used to guide the selection and titration of therapeutic agents (495). 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 (280, 496). Regardless of whether invasive hemodynamic monitoring is used, once the clinical status of the patient has stabilized, every effort should be made to devise an oral regimen that can maintain symptomatic improvement

and reduce the subsequent risk of deterioration. Assessment of the adequacy and tolerability of orally based strategies may necessitate observation in the hospital for at least 48 hours after the infusions are discontinued (497).

Patients who cannot be weaned from intravenous to oral therapy despite repeated attempts may require placement of an indwelling intravenous catheter to allow for the continuous infusion of dobutamine or milrinone, or as has been used more recently, nesiritide. Such a strategy is commonly used in patients who are awaiting cardiac transplantation, but it may also be used in the outpatient setting in patients who otherwise cannot be discharged from the hospital. The decision to continue intravenous infusions at home should not be made until all alternative attempts to achieve stability have failed repeatedly, because such an approach can present a major burden to the family and health services and may ultimately increase the risk of death. However, continuous intravenous support can provide palliation of symptoms as part of an overall plan to allow the patient to die with comfort at home (498, 499). The use of continuous intravenous support to allow hospital discharge should be distinguished from the intermittent administration of infusions of such agents to patients who have been successfully weaned from inotropic support.

4.4.4. 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 (500, 501). Current indications for cardiac transplantation focus on the identification of patients with severe functional impairment or dependence on intravenous inotropic agents (Table 10). Less common indications for cardiac transplantation include recurrent life-threatening ventricular arrhythmias or angina that is refractory to all currently available treatments (502).

Alternate surgical and mechanical approaches for the treatment of end-stage HF are under development. Clinical improvement has been reported after mitral valve repair or replacement in patients who have a clinically important degree of mitral regurgitation that is secondary to LV dilatation (120). However, no controlled studies have evaluated the effects of this procedure on ventricular function, clinical status, or survival. One recent single-center report of a non-randomized series of patients considered appropriate candidates for mitral valve repair did not demonstrate a survival advantage (503).

Although both cardiomyoplasty and left ventriculectomy (Batista procedure) at one time generated considerable excitement as potential surgical approaches to the treatment of refractory HF (504, 505), these procedures failed to result in clinical improvement and were associated with a high risk of death (506). A variant of the aneurysmectomy procedure is now being developed for the management of patients with ischemic cardiomyopathy (420), but its role in the management of HF remains to be defined. None of the current sur-

Table 10. Indications for Cardiac Transplantation**Absolute indications in appropriate patients**

For hemodynamic compromise due to HF

- Refractory cardiogenic shock
- Documented dependence on IV inotropic support to maintain adequate organ perfusion
- Peak VO_2 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 indicationsPeak VO_2 11 to 14 mL per kg per min (or 55% of 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 VO_2 greater than 15 mL per kg per min (and greater than 55% of predicted) without other indicationsHF indicates heart failure; IV, intravenous; and VO_2 , oxygen consumption per unit time.

gical reconstruction techniques offer “rescue therapy” to patients with critical hemodynamic compromise.

The use of mechanical circulatory assist devices in end-stage HF is an area of intense investigation. Extracorporeal devices can be used for short-term circulatory support in patients who are expected to recover from a major cardiac insult (e.g., myocardial ischemia, postcardiotomy shock, or fulminant myocarditis). Left ventricular assist devices provide similar degrees of hemodynamic support; many are implantable and thus allow for long-term support, patient ambulation, and hospital discharge (507). Most clinical experience with these devices has been derived from their use in patients being “bridged” to transplant. The completion of the Randomized Evaluation of Mechanical Assistance for the Treatment of Congestive Heart Failure (REMATCH) trial investigated the use of these devices as permanent or “destination” therapy in selected non-transplant-eligible patients. This trial enrolled 129 patients, for whom 2-year survival was 23% in the 68 patients treated with the device and 8% in the 61 patients who received medical therapy (508). Device-related adverse events were numerous and included bleeding, infection, thromboembolic events, and device failure. This trial established the efficacy of device therapy for end-stage HF. Improvements in newer generations of devices will hopefully permit even further prolongation of survival. Presently, destination device therapy is anticipated to benefit those patients predicted to have a 1-year survival of less than 50%. One such group could be the population of non-transplant-eligible patients requiring continuous intravenous inotropic infusions. Some reports have suggested that prolonged mechanical decompression of the failing heart may

occasionally be followed by sufficient recovery of myocardial function to allow explantation of the device (509). Improvements in ventricular mechanics, myocardial energetics, histology, and cell signaling have been reported with LV assist device support. However, the frequency and duration of myocardial recovery have been variable (510), and sufficient recovery to permit device explantation is rare except in a few patients with acute onset of HF and the absence of coronary artery disease. Coupling of device therapy with cell transplantation and a variety of angiogenesis or myocardial growth factors are approaches planned for future investigation.

5. TREATMENT OF SPECIAL POPULATIONS

RECOMMENDATIONS

Class I

1. **Groups of patients including (a) high-risk ethnic minority groups (e.g., blacks), (b) groups underrepresented in clinical trials, and (c) any groups believed to be underserved should, in the absence of specific evidence to direct otherwise, have clinical screening and therapy in a manner identical to that applied to the broader population. (Level of Evidence: B)**
2. **It is recommended that evidence-based therapy for HF be used in the elderly patient, with individualized consideration of the elderly patient's altered ability to metabolize or tolerate standard medications. (Level of Evidence: C)**

Class IIa

The addition of isosorbide dinitrate and hydralazine to a standard medical regimen for HF, including ACEIs and beta-blockers, is reasonable and can be effective in blacks with NYHA functional class III or IV HF. Others may benefit similarly, but this has not yet been tested. (Level of Evidence: A)

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

5.1. Women and Men

Many physicians regard HF primarily as a disease of men, because coronary risk factors are common in men and 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 a normal LVEF (27). Even HF due to reduced LVEF 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 ACEIs in women with HF than in men (511), and another study reported that

women are given fewer cardiovascular medications after an MI than men (510, 512, 513). 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 (510). Some analyses have suggested that women with HF, particularly with asymptomatic reduced LVEF, may not show survival benefits from ACE inhibition (514, 515). Women may also have a different safety profile than men, as evidenced by their higher risk of ACEI-induced cough (516). The conflicting data regarding the efficacy of digoxin in women suggests that if it is prescribed, particular attention should be paid to dosing and renal function (314). 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 a phosphodiesterase type 5 inhibitor (e.g., 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 HF 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 (517). 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 guanosine monophosphate (518).

5.2. Ethnic Considerations

Race is an imprecise concept that has largely become a social and political construct, with more limited biological significance (519). The concept of racial "minorities" may be relevant to large populations, especially those in clinical trials, but is clearly not a concept applicable in many demographic areas and clinical practices. However, it is useful to review epidemiological and clinical trial evidence to raise awareness of potential areas of concern and guide socioeconomic and clinical remedies. This has become especially pertinent in the evaluation of HF as it affects blacks, although much more information is also needed about the effects of current and new therapies in the Hispanic population. Heart failure is a major public health problem in blacks. Heart failure is more common in the black population, affecting approximately 3% of all black adults. This reflects a 50% higher incidence of HF in the black population than is seen in the general population.

Black patients develop symptoms of HF at an earlier average age than nonblacks, possibly because black patients are more likely to have hypertension and diabetes mellitus than nonblacks 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 hospitalizations (520-522). This risk cannot be explained by the presence of epicardial coronary artery disease or documented MI, both of which are less common in black than in nonblack patients with HF. The data are not clear as to whether a definitive increase in mortality risk exists (520-522).

The literature is mixed on whether blacks with HF more frequently receive suboptimal inpatient care for their HF (523, 524). However, deficiencies in cardiovascular risk factor evaluation and disease detection and treatment as well as in access to quality outpatient care may contribute to the increased incidence and morbidity of blacks with HF (525-527).

Blacks and other racial minorities with HF are underrepresented in most clinical trials of HF, which compromises the extrapolation of results from major clinical trials to ethnic subgroup populations. To date, there are no data to suggest that any significant treatment variance from standard care for HF should be acceptable in any particular group. Clinical experience suggests that Asian patients have a higher than average risk of cough during treatment with an ACEI. Retrospective analysis of subgroup data has suggested that, as in the treatment of hypertension, black patients with HF may experience less efficacy than nonblacks from the use of ACEIs (528). A recent analysis of a large ACEI HF trial that used a matched-cohort design confirmed that black patients had a greater number of hospitalizations for HF than matched white patients (529). However, rates of death in that trial were similar between black and nonblack patients with HF (529). 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 deaths and hospitalizations in nonblack patients (530). Thus, bucindolol may represent a decidedly different beta-blocker than those already approved for the treatment of HF. Conversely, the benefit of carvedilol in a separate series of trials was apparent and of a similar magnitude in both black and nonblack patients with HF (531). There may be race-based differences in the outcome of cardiac transplantation as well (532). Further study is needed to clarify these issues.

The emerging field of genomic medicine has begun to suggest that important variances in the expression of certain high-risk, single-nucleotide polymorphisms may be evident along racial lines and may provide a physiological basis for differences in the natural history of HF and differences in drug responsiveness (533-536). Data from these early investigations are not yet definitive; racial groupings are necessarily heterogeneous, and data will need to be interpreted cautiously.

A prospective, double-blind randomized trial conducted specifically in blacks with NYHA class III/IV HF has been completed (356). The patient population was characterized by a much higher likelihood of a nonischemic cause of HF

and of a history of hypertension and obesity. In this trial, the adjunctive use of a proprietary formulation of isosorbide dinitrate and hydralazine along with a standard HF regimen resulted in a 43% decrease in total mortality, which led to premature termination of the trial. Additionally, time to first hospitalization and quality of life were both improved. The mechanism of benefit of this regimen may be related to an improvement in nitric oxide bioavailability, but this regimen had a small (but significant) effect on blood pressure lowering. The effect of this combination of isosorbide dinitrate and hydralazine in other patients with HF who are undergoing standard therapy is not known because the population studied was limited to blacks, but there is no reason to believe that this benefit is limited to blacks (356).

5.3. Elderly Patients

Heart failure is particularly common in elderly patients. The prevalence of HF rises from 2% to 3% at age 65 to more than 80% in persons over 80 years of age (537), and HF is the most common reason for hospitalization in elderly patients (538-541). The high prevalence of HF in the elderly may be associated with age-related changes in ventricular function (particularly diastolic function) and to the cumulative effects of hypertension and other chronic risk factors (542-546). In addition, risk factors for HF (e.g., hypertension, diabetes mellitus, and 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) (132).

Heart failure in elderly patients is inadequately recognized and treated (547). Both patients and physicians frequently attribute the symptoms of HF to aging, and noninvasive cardiac imaging commonly fails to reveal impaired systolic function because HF with a preserved LVEF is frequently found in the elderly. In addition, some reports suggest that elderly patients may have diminished responses to diuretics, ACEIs, and positive inotropic agents (548, 548-550) compared with younger patients and may experience a higher risk of adverse effects attributable to treatment (513, 551-555). 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 (143, 556). Managed care organizations continue to struggle to find improved ways to implement these pathways (557, 558).

6. PATIENTS WITH HF WHO HAVE CONCOMITANT DISORDERS

RECOMMENDATIONS

Class I

1. All other recommendations should apply to patients with concomitant disorders unless there are specific exceptions. (*Level of Evidence C*)

2. Physicians should control systolic and diastolic hypertension and diabetes mellitus in patients with HF in accordance with recommended guidelines. (*Level of Evidence: C*)
3. Physicians should use nitrates and beta-blockers for the treatment of angina in patients with HF. (*Level of Evidence: B*)
4. Physicians should recommend coronary revascularization according to recommended guidelines in patients who have both HF and angina. (*Level of Evidence: A*)
5. Physicians should prescribe anticoagulants in patients with HF who have paroxysmal or persistent atrial fibrillation or a previous thromboembolic event. (*Level of Evidence: A*)
6. Physicians should control the ventricular response rate 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*)
7. Patients with coronary artery disease and HF should be treated in accordance with recommended guidelines for chronic stable angina. (*Level of Evidence: C*)
8. Physicians should prescribe antiplatelet agents for prevention of MI and death in patients with HF who have underlying coronary artery disease. (*Level of Evidence: B*)

Class IIa

1. It is reasonable to prescribe digitalis to control the ventricular response rate in patients with HF and atrial fibrillation. (*Level of Evidence: A*)
2. It is reasonable to prescribe amiodarone to decrease recurrence of atrial arrhythmias and to decrease recurrence of ICD discharge for ventricular arrhythmias. (*Level of Evidence: C*)

Class IIb

1. The usefulness of current strategies to restore and maintain sinus rhythm in patients with HF and atrial fibrillation is not well established. (*Level of Evidence: C*)
2. The usefulness of anticoagulation is not well established in patients with HF who do not have atrial fibrillation or a previous thromboembolic event. (*Level of Evidence: B*)
3. The benefit of enhancing erythropoiesis in patients with HF and anemia is not established. (*Level of Evidence: C*)

Class III

1. Class I or III antiarrhythmic drugs are not recommended in patients with HF for the prevention of ventricular arrhythmias. (*Level of Evidence: A*)
2. The use of antiarrhythmic medication is not indicated as primary treatment for asymptomatic ventricular

arrhythmias or to improve survival in patients with HF. (Level of Evidence: A)

Patients with reduced LVEF frequently have associated cardiovascular and noncardiovascular disorders, the course or treatment of which 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.

6.1. Cardiovascular Disorders**6.1.1. 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 (559). Both disorders can contribute to the development of systolic or diastolic dysfunction (560, 561), either directly or by contributing (together with hyperlipidemia) to the development of coronary artery disease (562, 563). Long-term treatment of both hypertension and hyperlipidemia decrease the risk of developing HF (55, 56, 564, 565). In a large-scale trial, the administration of a lipid-lowering agent to patients with hypercholesterolemia and a history of MI reduced all-cause mortality and the risk of developing HF (564). 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 (55, 56, 565). The benefits of lowering blood pressure may be particularly marked in patients with diabetes mellitus (63, 66, 566).

Heart failure may complicate the management of both hypertension and diabetes mellitus. Some 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 (567, 568), and the resulting hyperinsulinemia may promote both cardiac and vascular hypertrophy (569-571) and thus may hasten the progression of HF. These mechanisms may compound the deleterious effects of accelerated atherosclerosis and altered energy metabolism on cardiac function and may help to explain why diabetic patients with HF have a worse prognosis than their nondiabetic counterparts (75).

Thiazolidinediones have been associated with increased peripheral edema and symptomatic HF in patients with underlying risk factors or known cardiovascular disease. The risk of developing edema with thiazolidinediones is dose related and is higher in diabetic patients who are taking concomitant insulin therapy. However, the incidence of thiazolidinedione-related fluid retention is low in patients with NYHA functional class I to II symptoms, in whom these drugs can be administered safely with careful monitoring for fluid retention. Initiation of these drugs is not recommended

in patients with NYHA functional class III to IV symptoms of HF. 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 (572, 573).

Recommendations Concerning Management.

Little is known about the benefits of treating hypertension, hypercholesterolemia, or diabetes mellitus in patients with established reduced LVEF 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) (564) 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 (55, 56, 564, 565). 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 LVEF, whose symptoms may respond particularly well to treatments that lower blood pressure (574, 575). Renal artery stenosis should be considered in patients with hypertension and HF, because renal artery stenting can treat both conditions.

Drugs that can both control blood pressure and treat HF should be preferred in patients with both conditions; this includes the use of diuretics, ACEIs, 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 mellitus. Angiotensin converting enzyme inhibitors and beta-blockers prevent the progression of HF in diabetic and nondiabetic patients (193, 260, 576). 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.

6.1.2. 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 an MI. Therefore, physicians should manage both the symptomatic and prognostic consequences of the patient's underlying coronary artery disease in accordance with contemporary guidelines.

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 (577). Both nitrates and beta-blockers can improve anginal symptoms and may produce hemodynamic and clinical benefits in patients with reduced LVEF, and thus, they are preferred if these conditions coexist (255, 260, 262, 578, 579). 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 (580).

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 (581-583). These drugs have not improved symptoms of HF or enhanced exercise tolerance (580-584), 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 LV dysfunction (114, 585-593). 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 (594).

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 (595, 596), and coronary artery bypass surgery has been shown to lessen angina and reduce the risk of death in patients who have multivessel disease, reduced LVEF, and stable angina (597) [see the ACC/AHA/ACP-ASIM Guidelines for the Management of Patients With Chronic Stable Angina (598) or the ACC/AHA 2004 Guideline Update for Coronary Artery Bypass Graft Surgery (29)].

Recommendations Concerning Management of Patients Without Angina.

In patients with a prior MI but without HF or angina, 4 types of interventions have been used to reduce the risk of reinfarction and death: neurohormonal antagonists such as ACEIs and beta-blockers (66, 103, 104, 109); drugs to address dyslipidemia, such as statins; antiplatelet drugs such as aspirin and clopidogrel (209, 211); and coronary revascularization (595). In patients who have had an MI and who have HF but not angina, the use of ACEIs and beta-blockers can also decrease the risk of reinfarction and death (106-108, 599, 600), 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 ischemic events in patients without HF. The role of aspirin in patients with HF has not been established (595), and concerns have been raised that it may attenuate the hemodynamic and survival benefits of ACEIs (202, 205, 206). For these reasons, the role of aspirin in preventing ischemic events in patients with chronic HF is controversial (see Section 4.3.1.2.2.1). Alternative antiplatelet agents (e.g., clopidogrel) may not interact adversely with ACEIs (204) and may have superior effects in preventing clinical events (211), but their ability to favorably affect outcomes in HF has not been demonstrated (see Section 4.3.1.2.2.1).

Surgical revascularization has been recommended for a certain subset of patients in other guidelines (29). 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 myocardium that appears on imaging to be viable but not contracting normally (601-603) and may also reduce the risk of a fatal coronary occlusion in patients with established multivessel disease (602). 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 (21, 604).

6.1.3. 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 treatable 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 (605-607).

Supraventricular tachyarrhythmias may exert adverse effects by 4 different mechanisms: 1) the loss of atrial enhancement of ventricular filling may compromise cardiac output; 2) the rapid heart rate may increase demand and decrease coronary perfusion (by shortening ventricular filling time); 3) the rapidity of ventricular response may diminish both cardiac contraction (by aggravating abnormalities of the force-frequency relation) (608, 609) and cardiac relaxation (610, 611); and 4) the stasis of blood in the fibrillating atria may predispose patients to pulmonary or systemic emboli. 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 (612). 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 (115, 116). 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 (613, 614). Specific care and initially low doses should be used when beta blockers are instituted to control heart rate in patients with clinical evidence of HF decompensation.

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 more effectively at rest than during exercise (299, 615). Hence, digitalis does not block the excessive exercise-induced tachycardia that may limit the functional capacity of patients with HF (297-299, 615). Beta-blockers are more effective than digoxin during exercise (297, 299) and are preferred because of their favorable effects on the natural history of HF (255, 260, 262). The combination of digoxin and beta-blockers may be more effective than beta-blockers alone for rate control. 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 (588, 590). If beta-blockers are ineffective or contraindicated in patients with atrial fibrillation and HF, amiodarone may be a useful alternative (616). Atrioventricular nodal ablation may be needed if tachycardia persists despite pharmacological therapy (325). Catheter intervention for pulmonary vein isolation has been most effective in patients without structural heart disease; the benefit for patients with established HF is not known. 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. Anticoagulation should be maintained in all patients with HF and a history of atrial fibrillation, regardless of whether sinus rhythm is achieved, because of the high rate of silent recurrence of atrial fibrillation with its attendant embolic risk (614).

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 (614), 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 (605). 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 (127, 326), which can increase the risk of death (323, 324, 327). Class III antiarrhythmic 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) (617, 618) and proarrhythmia (dofetilide) (619). The efficacy and safety of restoring and maintaining sinus rhythm in patients with atrial fibrillation was recently evaluated in a total of 5032 patients in 4 separate trials (620). These trials consistently showed no improvement in mortality or morbidity using a strategy of

aggressive rhythm control. The trial populations did not include patients with HF symptoms associated with their atrial fibrillation. However, the rate-control strategy was associated with fewer hospitalizations and fewer side effects from drug therapy. Most patients who had thromboembolic events, regardless of the strategy used, were in atrial fibrillation at the time of the event and were either not undergoing anticoagulation therapy or were undergoing therapy at subtherapeutic levels. There was a subset analysis of patients with HF and atrial fibrillation that suggested better outcomes for those in whom sinus rhythm could be maintained. A further study is in progress (621). Until more definitive data are available, treatment must be individualized.

6.1.4. Prevention of Thromboembolic Events

Patients with chronic HF are at increased risk of thromboembolic events due to stasis of blood in dilated hypokinetic cardiac chambers and in peripheral blood vessels (622, 623) and perhaps due to increased activity of procoagulant factors (624). However, in large-scale studies, the risk of thromboembolism in clinically stable patients has been low (1% to 3% per year), even in those with very depressed EFs and echocardiographic evidence of intracardiac thrombi (625-629). These rates are sufficiently low to limit the detectable benefit of anticoagulation in these patients.

In several retrospective analyses, the risk of thromboembolic events was not lower in patients with HF taking warfarin than in patients not treated with antithrombotic drugs (625, 627, 628). 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 (630-632). A randomized trial comparing the outcome of patients with HF and low EF assigned to aspirin, warfarin, or clopidogrel was completed recently. Unfortunately, low enrollment in the trial precluded definitive conclusions about efficacy, but no therapy appeared to be superior. Another trial is currently under way comparing aspirin with warfarin in patients with reduced LVEF and may provide more definitive data upon which to base recommendations.

Recommendations Concerning Management.

In the absence of definitive trials, it is not clear how anticoagulants should be prescribed in patients with HF. Despite the lack of supportive data, some physicians prescribe anticoagulants to all patients with markedly depressed EFs and dilated hearts (622). Others would advocate the use of warfarin in patients who are known to harbor a cardiac thrombus (623), even though many thrombi detected by echocardiography do not embolize and many embolic events are probably related to thrombi that are not visualized (179, 633). Anticoagulation with warfarin is most justified in patients with HF who have experienced a previous embolic event or who have paroxysmal or persistent atrial fibrillation (614). Anticoagulation should also be considered in patients with underlying disorders that may be associated with an

increased thromboembolic risk (e.g., amyloidosis or LV non-compaction) and in patients with familial dilated cardiomyopathy and a history of thromboembolism in first-degree relatives.

6.2. Noncardiovascular Disorders

6.2.1. 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 ACEIs (161, 634) and are at increased risk of adverse effects during treatment with digitalis (304). Renal function may worsen during treatment with diuretics or ACEIs (160, 488), although the changes produced by these drugs are frequently short-lived, 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 (19, 635). The symptoms of HF in patients with end-stage renal disease may be exacerbated by an increase in loading conditions produced both by anemia (636) and by fistulas implanted to permit dialysis. In addition, toxic metabolites and abnormalities of phosphate, thyroid, and parathyroid metabolism associated with chronic renal insufficiency can depress myocardial function.

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 usually 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 (161, 304, 634). 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 (490, 637).

6.2.2. 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 these disorders coexist. 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 (638).

Some drugs used to treat HF can produce or exacerbate pulmonary symptoms. Angiotensin converting enzyme inhibitors can cause a persistent nonproductive cough that can be confused with a respiratory infection, and conversely,

ACEIs 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 ACEI. The cough should be attributed to the ACEI only if respiratory disorders have been excluded and the cough disappears after cessation of ACEI therapy and recurs after reinstatement of treatment. Because the ACEI-related cough does not represent any serious pathology, many patients can be encouraged to tolerate it in view of the important beneficial effects of ACEIs.

Beta-blockers can aggravate bronchospastic symptoms in patients with asthma; however, many patients with asymptomatic or mild reactive airways disease tolerate beta-blockers well. Also, most patients with chronic obstructive pulmonary disease do not have a bronchospastic component to their illness and remain reasonable candidates for beta-blockade (639). Of note, both metoprolol tartrate and bisoprolol may lose their beta-1 selectivity when prescribed in doses that have been associated with an improvement in survival in patients with HF.

6.2.3. 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 (640), high-dose cyclophosphamide (641-645), and trastuzumab (646). Trastuzumab is a monoclonal antibody recently approved for therapy of metastatic breast cancer (647) 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 (648).

Patients undergoing potentially cardiotoxic treatments for cancer should be monitored closely for the development of cardiac dysfunction. Heart failure may appear many years after anthracycline exposure, particularly in association with another stress, such as tachycardia. Although noninvasive assessments of LV function and endomyocardial biopsy have been advocated by some investigators (649), 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 (650, 651). 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 with other causes of HF. 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. Although once thought to progress inexorably, HF related to chemotherapy often improves in response to therapy, even when it appears late after exposure.

6.2.4. Patients With Thyroid Disease

Patients with both hyperthyroidism and hypothyroidism are prone to develop HF. Special vigilance is required for patients who are taking amiodarone, who may develop either hyperthyroidism or hypothyroidism. New atrial fibrillation or exacerbation of ventricular arrhythmias should trigger re-evaluation of thyroid status.

6.2.5. Patients With Hepatitis C and HIV

Hepatitis C viral infection can be a cause of cardiomyopathy and myocarditis. It appears that the virus can cause both dilated cardiomyopathy and hypertrophic cardiomyopathy (474, 475). The relatively high prevalence of this virus in Japanese populations compared with those in North America and Europe suggests that there may be a genetic predisposition to this type of viral myocarditis (476, 652). A small study showed that hepatitis C virus myocarditis might respond favorably to immunosuppressive therapy with prednisone and azathioprine (653, 654). Preliminary data also suggest that this type of myocarditis might respond well to interferon therapy (475), although there is concern that interferon can also depress myocardial function.

Human immunodeficiency virus has been recognized as a probable occasional cause of dilated cardiomyopathy. The presence of reduced LVEF in patients with HIV infection appears to correlate with decreased survival (655). Reduced LVEF is often seen in association with a significantly reduced CD4 count, although progression of cardiomyopathy does not appear to be related to falling CD4 levels (656). Drug therapy for HIV with zidovudine has also been implicated as a cause of cardiomyopathy, possibly through its effect on cardiac myocyte mitochondrial function (657). Heart failure in patients with HIV infection may also be caused or exacerbated by pericardial effusion or pulmonary hypertension. Interferon-alpha therapy for HIV-related Kaposi's sarcoma has also been associated with reversible reduction in LVEF. Because of the occurrence of complex opportunistic infections, autoimmune responses to the viral infection, and drug cardiotoxicity, it is difficult to determine how therapies influence the development and control of cardiomyopathy with HIV (658).

6.2.6. Patients With Anemia

Anemia is seldom the cause of HF in the absence of underlying cardiac disease. To be the sole cause of high-output HF, anemia must be severe (e.g., hemoglobin levels less than 5 g per deciliter). On the other hand, patients with HF frequently have anemia for a variety of reasons. The severity of anemia may contribute to the increasing severity of HF. Several studies have demonstrated worse outcomes in patients with HF and anemia (659, 660). It is unclear whether anemia is the cause of decreased survival or a result of more severe disease.

Several small studies have suggested benefit from use of erythropoietin and iron for treatment of mild anemia in HF (661-663). There is concern, however, that thromboembolic

events may be increased. This therapy is undergoing further investigation.

7. END-OF-LIFE CONSIDERATIONS

RECOMMENDATIONS

Class I

1. Ongoing patient and family education regarding prognosis for functional capacity and survival is recommended for patients with HF at the end of life. (*Level of Evidence: C*)
2. Patient and family education about options for formulating and implementing advance directives and the role of palliative and hospice care services with re-evaluation for changing clinical status is recommended for patients with HF at the end of life. (*Level of Evidence: C*)
3. Discussion is recommended regarding the option of inactivating ICDs for patients with HF at the end of life. (*Level of Evidence: C*)
4. It is important to ensure continuity of medical care between inpatient and outpatient settings for patients with HF at the end of life. (*Level of Evidence: C*)
5. Components of hospice care that are appropriate to the relief of suffering, including opiates, are recommended and do not preclude the options for use of inotropes and intravenous diuretics for symptom palliation for patients with HF at the end of life. (*Level of Evidence: C*)
6. All professionals working with HF patients should examine current end-of-life processes and work toward improvement in approaches to palliation and end-of-life care. (*Level of Evidence: C*)

Class III

Aggressive procedures performed within the final days of life (including intubation and implantation of a cardioverter-defibrillator in patients with NYHA functional class IV symptoms who are not anticipated to experience clinical improvement from available treatments) are not appropriate. (*Level of Evidence: C*)

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

reasonable expectation of a return to good functional capacity.

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 (664). These frequencies are higher than those seen in other chronic diseases (665), 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 in the United States are required by the Patient Self-Determination Act (666) 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 (667). The majority of patients with HF who had not discussed resuscitation during hospitalization indicated that they had not desired such an interaction (664). 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 unexpected cardiac arrests compared with more than 25% of patients in intensive care units who had other chronic illnesses (668).

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 supportive care while conscious, other than actual resuscitation; in other circumstances, hospitalization may no longer be desired for any intervention. Any decision to forego resuscitation should lead to possible deactivation of the life-saving function of an implanted defibrillation device; the poor functional status of any patient should also influence the decision regarding implantation of such a device in the first place (669). To observe both the intent and the directives of the patient and family, it is highly desirable that outpatient, inpatient, and crisis management be supervised by the same team to diminish the hazards of fragmented care during this period. The patient should be encouraged to choose in advance a person to assume legal authority (i.e., designated power of attorney or healthcare proxy) for healthcare matters when the patient cannot be involved in decisions. That individual should serve as the contact point for the team. Rapid communications with this team will reduce the conflicts and uncertainties that may arise when patients are first seen in an 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. Professionals caring for patients with advanced HF should have realistic expectations for survival and communicate those accurately to patients and families. Also, the professionals should provide realistic

recommendations for procedures being done within the final days of life that do not add to the hope of recovery or improvement in life quality. Finally, greater attention and research need to be devoted to the provision of comfort measures in the final days of life, including relief of pain and dyspnea.

Hospice services have only recently been extended to patients dying of HF. Originally developed for patients with end-stage cancer, the focus of hospice care has now been expanded to include the relief of symptoms other than pain (670). This is appropriate because the suffering of patients with HF is characteristically linked to symptoms of breathlessness, and thus, compassionate care may require the frequent administration of intravenous diuretics and, in some cases, the continuous infusion of positive inotropic agents rather than only the use of potent analgesics. However, many patients dying of HF do describe pain during the final days (671, 672). Physicians caring for these patients should become familiar with the prescription of anxiolytics, sleeping medications, 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 healthcare providers are generally unable to accurately predict the end of life in patients with HF. In a large US study on the 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 (673). 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 (674) are being revised to allow patients with HF to benefit from the type of care that can be provided through hospice services.

Ultimately, the decisions regarding when end of life is nearing reflect a complex interaction between objective information and subjective information, emotions, and patient and family readiness. Ideally, these decisions would be made in conjunction with the individual or team most experienced in caring for advanced HF or in collaboration and/or consultation with such an expert. In reality, however, this does not occur often. The Writing Committee recommends that all those involved with HF care make it a priority to improve recognition of end-stage disease and provide care to patients and families approaching this stage. As we become more familiar with the steps in progression to end-stage HF in this era, the current abrupt transition from aggressive intervention to comfort and bereavement care will be softened by a gradual and progressive emphasis on palliation until it dominates the final days of care (672).

8. IMPLEMENTATION OF PRACTICE GUIDELINES RECOMMENDATIONS

Class I

1. Academic detailing or educational outreach visits are useful to facilitate the implementation of practice guidelines. (*Level of Evidence: A*)
2. Multidisciplinary disease-management programs for patients at high risk for hospital admission or clinical deterioration are recommended to facilitate the implementation of practice guidelines, to attack different barriers to behavioral change, and to reduce the risk of subsequent hospitalization for HF. (*Level of Evidence: A*)

Class IIa

1. Chart audit and feedback of results can be effective to facilitate implementation of practice guidelines. (*Level of Evidence: A*)
2. The use of reminder systems can be effective to facilitate implementation of practice guidelines. (*Level of Evidence: A*)
3. The use of performance measures based on practice guidelines may be useful to improve quality of care. (*Level of Evidence: B*)
4. Statements by and support of local opinion leaders can be helpful to facilitate implementation of practice guidelines. (*Level of Evidence: A*)

Class IIb

Multidisciplinary disease-management programs for patients at low risk for hospital admission or clinical deterioration may be considered to facilitate implementation of practice guidelines. (*Level of Evidence: B*)

Class III

1. Dissemination of guidelines without more intensive behavioral change efforts is not useful to facilitate implementation of practice guidelines. (*Level of Evidence: A*)
2. Basic provider education alone is not useful to facilitate implementation of practice guidelines. (*Level of Evidence: A*)

Despite the publication of evidence-based guidelines (147, 675), the current care of patients with HF remains suboptimal. Numerous studies document underutilization of key processes of care, such as use of ACEIs in patients with decreased systolic function and the measurement of LVEF (513, 676, 677). 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 (491, 678, 679). Many HF admissions may be prevented with good outpatient care (680). The literature on

implementing practice guidelines for patients with HF can be divided into 3 areas: isolated provider interventions, disease-management systems, and use of performance measures.

8.1. 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 (681). Indeed, an extensive literature has documented how difficult it is to produce appropriate changes in physician behavior (682-684). 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 (685). 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.

8.2. 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 (146, 686). 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 (687). 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 MI or uncontrolled hypertension (143). 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.

8.3. Performance Measures

Performance measures are standards of care for a particular illness or condition that are designed to assess and subsequently improve the quality of medical care. Performance measures are chosen on the basis of the knowledge or assumption that the particular item is linked to improved patient outcomes. In the field of HF, such measures might include documentation of the level of LV function, medications used, or patient education measures. These measures can be used either internally within an organization or publicly to compare the performance of providers, hospitals, and healthcare organizations. In theory, performance measures could improve care by encouraging providers to compete on the basis of quality as opposed to cost, empowering consumers to make informed choices in the marketplace, providing incentives to providers to concentrate on certain diseases or processes of care, and supplying information to aid with internal quality improvement. The evidence is mixed, but some studies indicate that performance measures can improve health outcomes (688).

The ACC and AHA are collaborating with a variety of organizations to develop and implement performance measures. ACC/AHA practice guidelines are useful starting points for performance measures, but several considerations apply: 1) ACC/AHA practice guidelines are designed for improving the care of individual patients. Performance measures are generally used for improving the care of populations of patients. Although significant overlap exists in these goals, performance measures need to take into account additional factors, such as ease of data collection, simplicity of standards, calculation of sufficient numbers of patients for whom the measure would apply, and provision of flexibility for clinically diverse situations. 2) In general, most performance measures should be chosen from Class I and Class III practice guideline recommendations; however, given the additional factors involved in improving the care of populations of patients, Class IIa recommendations may be suitable in selected situations. 3) Opportunities should be given for clinicians to describe why a particular performance measure may not be appropriate for an individual patient.

8.4. 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 (689-691). Some studies have noted better patient outcomes in patients cared for by cardiologists than in those cared for by generalist physicians (692, 693), whereas another study reported that cardiologists deliver more costly care that is accompanied by a trend toward improved survival (694). 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 healthcare 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.

STAFF

American College of Cardiology

Christine W. McEntee, Chief Executive Officer
Marie J. Temple, Specialist, Practice Guidelines
Joseph M. Allen, MA, Director, Clinical Decision Support

American Heart Association

M. Cass Wheeler, Chief Executive Officer
Rose Marie Robertson, MD, FACC, FAHA, Chief Science Officer
Kathryn A. Taubert, PhD, FAHA, Senior Science Advisor

APPENDIX 1. ACC/AHA Committee to Revise the 2001 Guidelines for the Evaluation and Management of Chronic Heart Failure—Relationships With Industry

Committee Member	Research Grant	Speakers Bureau	Stock Ownership	Board of Directors	Consultant/ Advisory Member
Dr. William T. Abraham	Amgen Biosite Biotronik Cardio Dynamics International Corp. Guidant Corp. Medtronic Myogen Orqis Medical Otsuka Maryland Research Institute Scios Vasogen Yamanouchi	GlaxoSmithKline Guidant Corp. Medtronic Merck & Co. Pfizer Scios St. Jude Medical	None	None	CHF Solutions GlaxoSmithKline Medtronic Scios
Dr. Marshall H. Chin	None	None	None	None	None
Dr. Arthur M. Feldman	Medtronic Myogen Orqis Pfizer Vasomedical	Astra-Zeneca Guidant	Cardiokine	Cardiokine	Astra-Zeneca Guidant Myogen Pfizer Vasomedical
Dr. Gary S. Francis	Pfizer	None	None	None	GlaxoSmithKline Merck Novartis
Dr. Theodore G. Ganiats	None	None	None	None	Pfizer
Dr. Sharon Ann Hunt	None	None	None	None	None
Dr. Mariell Jessup	Medtronic Novartis Pfizer	GlaxoSmithKline Medtronic	None	None	ACORN GlaxoSmithKline Medtronic
Dr. Marvin A. Konstam	GlaxoSmithKline	Astra-Zeneca GlaxoSmithKline Merck Novartis	None	None	Astra-Zeneca GlaxoSmithKline Merck Novartis
Dr. Donna M. Mancini	None	None	None	None	None
Dr. Keith A. Michl	None	None	None	None	None
Dr. John A. Oates	Merck McNeil	None	None	None	Merck McNeil
Dr. Peter S. Rahko	Bristol-Myers Squibb Myogen Novartis	Boehringer-Ingelheim Novartis Pfizer	None	None	GlaxoSmithKline
Dr. Marc A. Silver	Pfizer Scios	GlaxoSmithKline	Cardiodynamics	None	None
Dr. Lynne Warner Stevenson	Medtronic	None	None	None	Medtronic Scios
Dr. Clyde W. Yancy	GlaxoSmithKline NitroMed Scios	GlaxoSmithKline Medtronic Novartis	None	None	CHF Solutions GlaxoSmithKline Medtronic Scios

This table represents the relationships of committee members with industry that were disclosed at the initial writing committee meeting in November 2003 and updated in conjunction with all meetings and conference calls of the writing committee. It does not necessarily reflect relationships with industry at the time of publication.

APPENDIX 2. External Peer Reviewers for the ACC/AHA 2005 Guideline Update for the Diagnosis and Management of Chronic Heart Failure in the Adult*

Peer Reviewer Name†	Representation	Research Grant	Speakers Bureau/Honoraria	Stock Ownership	Consultant/Advisory Board
Dr. Mihai Gheorghiade	Official Reviewer - AHA	GlaxoSmithKline Otzuka Sigma Tau	Pfizer	None	GlaxoSmithKline Medtronic Otzuka Sigma Tau
Dr. Jonathan L. Halperin	Official Reviewer - ACC/AHA Task Force Lead Review	None	Astra-Zeneca Bristol-Myers Squibb/ Sanofi Partnership	None	Astra-Zeneca Bayer AG Boehringer Ingelheim Bristol-Myers Squibb/Sanofi Partnership
Dr. Jagat Narula	Official Reviewer - AHA	None	None	None	None
Dr. Milton Packer	Official Reviewer - ACC/AHA	None	None	Discovery Laboratories Titan Pharmaceuticals	Abbott Astra-Zeneca Actelion Cardiodynamics Discovery Laboratories GlaxoSmithKline Orion Pharmaceuticals Titan Pharmaceuticals Yamanouchi
Dr. Ileana L. Pina	Official Reviewer - AHA	Biosite CMS NIH	Astra-Zeneca GlaxoSmithKline Novartis Pfizer	None	Astra-Zeneca FDA - CDRH
Dr. Miguel A. Quinones	Official Reviewer - ACCF Board of Trustees	None	None	None	Proctor & Gamble
Dr. Richard F. Wright	Official Reviewer - ACCF Board of Governors	None	Astra-Zeneca Bristol-Myers Squibb Novartis	Cardiodynamics	Bristol-Myers Squibb Cardiodynamics Novartis
Nancy M. Albert, CNS	Content Reviewer - AHA HF and Transplantation Committee	None	Medtronic GlaxoSmithKline Scios Pharmaceuticals	None	GlaxoSmithKline
Dr. Jeffrey L. Anderson	Content Reviewer - Individual Review	None	Merck Johnson & Johnson Merck-Schering-Plough	None	Merck Johnson & Johnson Merck-Schering-Plough
Dr. Elliott M. Antman	Content Reviewer - Individual Review	Astra-Zeneca Biosite Boehringer-Mannheim Bristol-Myers Squibb Centocor CV Therapeutics Dade Dendrion Eli Lilly Genentech Merck Millennium Sanofi-Aventis Sunol Molecular	None	None	None

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*Participation in the peer review process does not imply endorsement of the document.

†Names are listed in alphabetical order within each category of review.

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APPENDIX 2. *Continued*^{*}

Peer Reviewer Name [†]	Representation	Research Grant	Speakers Bureau/ Honoraria	Stock Ownership	Consultant/ Advisory Board
Dr. Malcolm O. Arnold	Content Reviewer - ACC HF Data Standards Committee	None	Aventis Merck-Frosst Novartis Pfizer	None	Aventis Merck-Frosst Novartis Pfizer
Dr. John P. Boehmer	Content Reviewer - Individual Review	Acorn Cardiovascular Amgen Cardiovascular Bio Therapeutics Guidant Medtronic Myogen Orion Pharmaceuticals	None	None	None
Dr. Michael R. Bristow	Content Reviewer - Individual Review	None	None	None	Astra-Zeneca Cardiac Dimensions Covalent C2R CVRx Genzyme GlaxoSmithKline Guidant Merck Mitsubishi Mylan Myogen Novartis Scios Pharmaceuticals
Dr. Alfred E. Buxton	Content Reviewer - ACC/AHA Ventricular Arrhythmias and Sudden Cardiac Death Guideline Committee	Medtronic Guidant St. Jude	None	None	Medtronic
Dr. Charles E. Canter	Content Reviewer - AHA Committee on HF and Transplantation	Novartis	None	None	None
Dr. Donald E. Casey	Content Reviewer - ACC HF Performance Measures Committee	None	None	None	None
Dr. Michael P. Cinquegrani	Content Reviewer - ACC HF Data Standards Committee	None	None	Medtronic Pfizer	None
Dr. Teresa De Marco	Content Reviewer - Individual Review	Scios Pharmaceuticals	Guidant Medtronic Scios Pharmaceuticals	None	Guidant Medtronic Scios Pharmaceuticals
Dr. Gordon A. Ewy	Content Reviewer - ACC/AHA Coronary Artery Bypass Graft Surgery Guideline Writing Committee	None	Astra-Zeneca Kos GlaxoSmithKline Merck Pfizer Schering-Plough Wyeth-Ayerst	None	None

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APPENDIX 2. Continued*

Peer Reviewer Name†	Representation	Research Grant	Speakers Bureau/Honoraria	Stock Ownership	Consultant/Advisory Board
Dr. Gregg C. Fonarow	Content Reviewer - AHA Quality of Care and Outcomes Committee	Amgen Biosite Bristol-Myers Squibb GlaxoSmithKline Guidant Medtronic Merck Pfizer Scios Pharmaceuticals	Amgen Biosite Bristol-Myers Squibb GlaxoSmithKline Guidant Medtronic Merck Pfizer Scios Pharmaceuticals	None	Amgen Biosite Bristol-Myers Squibb GlaxoSmithKline Guidant Medtronic Merck Pfizer Scios Pharmaceuticals
Dr. Michael M. Givertz	Content Reviewer - AHA Committee on HF and Transplantation	None	None	None	None
Dr. David C. Goff	Content Reviewer - AHA Quality of Care and Outcomes Committee	None	Pfizer	None	Johnson & Johnson Pfizer
Dr. Edward P. Havranek	Content Reviewer - ACC HF Data Standards Committee	None	None	None	None
Dr. Paul A. Heidenreich	Content Reviewer - ACC HF Data Standards Committee	None	None	None	None
Dr. Mark A. Hlatky	Content Reviewer - ACC HF Performance Measures Committee	None	None	None	None
Dr. Judith S. Hochman	Content Reviewer - ACC/AHA ST-Elevation Myocardial Infarction Guideline Writing Committee	Arginox Eli Lilly	None	None	Datascope Diachii Millennium Proctor and Gamble Sanofi-Aventis
Dr. Marrick L. Kuckin	Content Reviewer - Individual Review	Astra-Zeneca Myogen Vasogen	Astra-Zeneca Myogen Vasogen	None	Astra-Zeneca
Dr. Barry M. Massie	Content Reviewer - Individual Review	None	None	None	None
Debra Moser, MN, RN	Content Reviewer - AHA Quality of Care and Outcomes Committee	None	None	None	None
Dr. Erik Magnus Ohman	Content Reviewer - Individual Review	Bristol-Myers Squibb/Sanofi Millennium Schering-Plough Berlex	None	Medtronic	None
Dr. Eric N. Prystowsky	Content Reviewer - ACC/AHA/ESC Atrial Fibrillation Guideline Writing Group	None	None	None	Guidant
Dr. Andrew L. Smith	Content Reviewer - ACC HF Performance Measures Committee	Guidant Medtronic NitroMed	Guidant Medtronic	None	None

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APPENDIX 2. *Continued**

Peer Reviewer Name†	Representation	Research Grant	Speakers Bureau/Honoraria	Stock Ownership	Consultant/Advisory Board
Dr. George Sopko	Content Reviewer - AHA Committee on HF and Transplantation	None	None	None	None
Dr. Karl T. Weber	Content Reviewer - Individual Review	None	None	None	None
Dr. William S. Weintraub	Content Reviewer - AHA Quality of Care and Outcomes Committee	Pfizer	Pfizer	None	Pfizer
Dr. Deborah Allen	Organizational - American Academy of Family Physicians	None	None	None	None
Dr. Denise Barnard	Organizational Reviewer - Heart Failure Society of America	None	None	None	None
Dr. Jonathan Howlett	Organizational Reviewer - Heart Failure Society of America	Astra-Zeneca	None	None	Astra-Zeneca Novartis Servier Merck Bristol-Myers Squibb/Sanofi
Dr. Ijaz A. Kahn	Organizational Reviewer - American College of Chest Physicians	None	None	None	None
Dr. JoAnn Lindenfeld	Organizational Reviewer - Heart Failure Society of America	Bristol-Myers Squibb/Sanofi Medtronic Myogen Novocardia Pfizer Scios Pharmaceuticals	None	None	None
Dr. Mandeep R. Mehra	Organizational Reviewer - International Society for Heart and Lung Transplantation	Astra-Zeneca Biosite Diagnostics Guidant Medtronic Merck Scios Pharmaceuticals	Astra-Zeneca Biosite Diagnostics Guidant Medtronic Merck Novartis Scios Pharmaceuticals	Hommed	Astra-Zeneca Biosite Diagnostics Guidant Medtronic Merck Novartis Scios Pharmaceuticals
Dr. Alan Miller	Organizational Reviewer - Heart Failure Society of America	Amgen Astra-Zeneca GlaxoSmithKline Myogen NitroMed Novartis Pfizer	Astra-Zeneca Bristol-Myers Squibb/Sanofi GlaxoSmithKline Novartis Pfizer Wyeth	None	GlaxoSmithKline Pfizer
Dr. K. Vijayaraghavan	Organizational Reviewer - American College of Chest Physicians	Amgen Astra-Zeneca Cardiodynamics Kos Merck-Schering-Plough Myogen Pfizer	GlaxoSmithKline Guidant Merck Medtronic Novartis Pfizer Scios Pharmaceuticals	None	None

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APPENDIX 3. ABBREVIATIONS

ACC	= American College of Cardiology
ACE	= angiotensin converting enzyme
ACEI	= angiotensin converting enzyme inhibitor
AHA	= American Heart Association
ARB	= angiotensin II receptor blocker
ATPase	= adenosine triphosphatase
BNP	= B-type natriuretic peptide*
CRT	= cardiac resynchronization therapy

EF	= ejection fraction
HF	= heart failure
HIV	= human immunodeficiency virus
ICD	= implantable cardioverter-defibrillator
LV	= left ventricular; left ventricle
LVEF	= left ventricular ejection fraction
LVH	= left ventricular hypertrophy
MI	= myocardial infarction
NYHA	= New York Heart Association
VT	= ventricular tachycardia

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

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ACC/AHA 2005 Guideline Update for the Diagnosis and Management of Chronic Heart Failure in the Adult: A Report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (Writing Committee to Update the 2001 Guidelines for the Evaluation and Management of Heart Failure): Developed in Collaboration With the American College of Chest Physicians and the International Society for Heart and Lung Transplantation: Endorsed by the Heart Rhythm Society
WRITING COMMITTEE MEMBERS, Sharon Ann Hunt, William T. Abraham, Marshall H. Chin, Arthur M. Feldman, Gary S. Francis, Theodore G. Ganiats, Mariell Jessup, Marvin A. Konstam, Donna M. Mancini, Keith Michl, John A. Oates, Peter S. Rahko, Marc A. Silver, Lynne Warner Stevenson, Clyde W. Yancy, Elliott M. Antman, Sidney C. Smith, Jr, Cynthia D. Adams, Jeffrey L. Anderson, David P. Faxon, Valentin Fuster, Jonathan L. Halperin, Loren F. Hiratzka, Sharon Ann Hunt, Alice K. Jacobs, Rick Nishimura, Joseph P. Ornato, Richard L. Page and Barbara Riegel

Circulation. 2005;112:e154-e235; originally published online September 13, 2005;
doi: 10.1161/CIRCULATIONAHA.105.167586

Circulation is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
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Print ISSN: 0009-7322. Online ISSN: 1524-4539

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