**2009 Focused Update Incorporated Into the ACC/AHA 2005 Guidelines for the Diagnosis and Management of Heart Failure in Adults: A Report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines Developed in Collaboration With the International Society for Heart and Lung Transplantation**

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, and Clyde W. Yancy

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**PRACTICE GUIDELINE: FULL TEXT**

# 2009 Focused Update Incorporated Into the ACC/AHA 2005 Guidelines for the Diagnosis and Management of Heart Failure in Adults

A Report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines

*Developed in Collaboration With the International Society for Heart and Lung Transplantation*

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## Preamble (UPDATED)

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 Foundation (ACCF) 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 ACCF/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 outcomes will constitute the primary basis for preparing recommendations in these guidelines.

The ACCF/AHA Task Force on Practice Guidelines makes every effort to avoid any actual, potential, or per-

**Table 1. Applying Classification of Recommendations and Level of Evidence**

| ESTIMATE OF CERTAINTY (PRECISION) OF TREATMENT EFFECT ↓ / SIZE OF TREATMENT EFFECT → | CLASS I<br>*Benefit >>> Risk*<br>Procedure/Treatment **SHOULD** be performed/ administered | CLASS IIa<br>*Benefit >> Risk*<br>*Additional studies with focused objectives needed*<br>**IT IS REASONABLE** to perform procedure/administer treatment | CLASS IIb<br>*Benefit ≥ Risk*<br>*Additional studies with broad objectives needed; additional registry data would be helpful*<br>Procedure/Treatment **MAY BE CONSIDERED** | CLASS III<br>*Risk ≥ Benefit*<br>Procedure/Treatment should **NOT** be performed/administered **SINCE IT IS NOT HELPFUL AND MAY BE HARMFUL** |
|---|---|---|---|---|
| **LEVEL A**<br>Multiple populations evaluated*<br>Data derived from multiple randomized clinical trials or meta-analyses | ■ Recommendation that procedure or treatment is useful/effective<br>■ Sufficient evidence from multiple randomized trials or meta-analyses | ■ Recommendation in favor of treatment or procedure being useful/effective<br>■ Some conflicting evidence from multiple randomized trials or meta-analyses | ■ Recommendation's usefulness/efficacy less well established<br>■ Greater conflicting evidence from multiple randomized trials or meta-analyses | ■ Recommendation that procedure or treatment is not useful/effective and may be harmful<br>■ Sufficient evidence from multiple randomized trials or meta-analyses |
| **LEVEL B**<br>Limited populations evaluated*<br>Data derived from a single randomized trial or nonrandomized studies | ■ Recommendation that procedure or treatment is useful/effective<br>■ Evidence from single randomized trial or nonrandomized studies | ■ Recommendation in favor of treatment or procedure being useful/effective<br>■ Some conflicting evidence from single randomized trial or nonrandomized studies | ■ Recommendation's usefulness/efficacy less well established<br>■ Greater conflicting evidence from single randomized trial or nonrandomized studies | ■ Recommendation that procedure or treatment is not useful/effective and may be harmful<br>■ Evidence from single randomized trial or nonrandomized studies |
| **LEVEL C**<br>Very limited populations evaluated*<br>Only consensus opinion of experts, case studies, or standard of care | ■ Recommendation that procedure or treatment is useful/effective<br>■ Only expert opinion, case studies, or standard of care | ■ Recommendation in favor of treatment or procedure being useful/effective<br>■ Only diverging expert opinion, case studies, or standard of care | ■ Recommendation's usefulness/efficacy less well established<br>■ Only diverging expert opinion, case studies, or standard of care | ■ Recommendation that procedure or treatment is not useful/effective and may be harmful<br>■ Only expert opinion, case studies, or standard of care |
| Suggested phrases for writing recommendations† | should<br>is recommended<br>is indicated<br>is useful/effective/beneficial | is reasonable<br>can be useful/effective/beneficial<br>is probably recommended or indicated | may/might be considered<br>may/might be reasonable<br>usefulness/effectiveness is unknown/unclear/uncertain or not well established | is not recommended<br>is not indicated<br>should not<br>is not useful/effective/beneficial<br>may be harmful |

*Data available from clinical trials or registries about the usefulness/efficacy in different subpopulations, such as gender, age, history of diabetes, history of prior myocardial infarction, history of heart failure, and prior aspirin use. A recommendation with Level of Evidence B or C does not imply that the recommendation is weak. Many important clinical questions addressed in the guidelines do not lend themselves to clinical trials. Even though randomized trials are not available, there may be a very clear clinical consensus that a particular test or therapy is useful or effective. †In 2003, the ACCF/AHA Task Force on Practice Guidelines developed a list of suggested phrases to use when writing recommendations. All guideline recommendations 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.

ceived 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. Writing committee members are also strongly encouraged to declare a previous relationship with industry that may be perceived as relevant to guideline development. If a writing committee member develops a new relationship during his or her tenure, he or she is required to notify the guideline writing staff in writing. The continued participation of the writing committee member will be 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 refer to the methodology manual for the ACCF/AHA guideline writing committees for further description and the relationships with industry policy (1). See Appendix 1 for a list of writing committee member relationships with industry and Appendix 2 for a listing of peer reviewer relationships with industry that are pertinent to this guideline.

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.

The 2005 guidelines were approved for publication by the governing bodies of the ACCF 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 summary article including recommendations was 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 (my.americanheart.org). Copies of the full text and the summary article are available from both organizations.

The current document is a re-publication of the "ACC/AHA 2005 Guideline Update for the Diagnosis and Management of Chronic Heart Failure in the Adult" (2), revised to incorporate updated recommendations and text from a focused update performed during 2008 (3). Recommendations have been updated with new information that has emerged from clinical trials or other ACCF/AHA guideline or consensus documents. In addition, the writing committee felt that a new section, the Hospitalized Patient, was necessary to address the increasingly recognized problem of the patient with acute decompensated heart failure, as opposed to the patient with chronic heart failure. Heart failure is now the single most common reason why patients over 65 years are admitted to the hospital, and the updated guidelines review important management principles for this population. For easy reference, this online-only version denotes sections that have been updated.

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## 1. Introduction (UPDATED)

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 (4). The disorder is the primary reason for 12 to 15 million office visits and 6.5 million hospital days each year (5). 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 (6). 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 (4).

Heart failure is primarily a condition of the elderly (7), 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 (4), and approximately 80% of patients hospitalized with HF are more than 65 years old (8). 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 (9). The total estimated direct and indirect costs for HF in 2005 were approximately $27.9 billion (4). In the United States, approximately $2.9 billion annually is spent on drugs for the treatment of HF (4).

### 1.1. Evidence Review (UPDATED)

The ACCF and the AHA first published guidelines for the evaluation and management of HF in 1995 and published revised guidelines in 2001 (10). 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 recommendations listed in the 2005 guideline 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.

In 2005, 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. Other guidelines are relevant to the HF population, and include the ACC/AHA Guidelines for the Management of Patients With ST-Elevation Myocardial Infarction (11) and the ACC/AHA 2002 Update of the Guidelines for the Management of Unstable Angina and Non-ST Elevation Myocardial Infarction (12). These guidelines have 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 [13]) or congenital malformations, and we have not included recommendations for the treat-

ment of specific myocardial disorders (e.g., hemochromatosis, sarcoidosis, or amyloidosis).

For the 2009 focused update, late-breaking clinical trials presented at the 2005, 2006, and 2007 annual scientific meetings of the ACCF, AHA, and European Society of Cardiology, as well as selected other data, from 2005 through November 2007, were reviewed by the standing guideline writing committee along with the parent task force to identify those trials and other key data that might impact guideline recommendations. On the basis of the criteria/considerations noted earlier, recent trial data and other clinical information were considered important enough to prompt a focused update of the ACCF/AHA 2005 Guideline Update for the Diagnosis and Management of Chronic Heart Failure in the Adult (2). In addition, the guidelines writing committee thought that a new section on the management of the hospitalized patient with HF should be included in this update. A number of recent HF trials reviewed for this update, were, in fact, performed on hospitalized patients, and a number of newer therapies are under development for this population. Moreover, there is increasing government and other third-party payer interest in the prevention of HF hospitalizations, and rehospitalizations. Quality indicators about the process of discharging the HF patient have already been developed, and data about rehospitalizations for HF by hospital have been made public. Thus, the committee thought that a new section about this important aspect of HF care should be added to the update.

When considering the new data for the focused update, the writing group faced the task of weighing evidence from studies enrolling large numbers of subjects outside North America. While noting that practice patterns and the rigor applied to data collection, as well as the genetic makeup of subjects, might influence the observed magnitude of a treatment's effect, the writing group believed that the data were relevant to formulation of recommendations for the management of HF in North America.

### 1.2. Organization of Committee and Relationships With Industry (UPDATED)

The 2005 writing committee was composed of 15 members who represented the ACCF 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.

For the 2009 focused update, all members of the 2005 HF writing committee were invited to participate; those who agreed (referred to as the 2009 Focused Update Writing Group) were required to disclose all relationships with industry relevant to the data under consideration (1) as were all peer reviewers of the document (see Appendixes 4 and 5 for a listing of relationships with industry for the 2009 Focused Update Writing Group and peer reviewers, respectively). Each recommendation required a confidential vote by the writing group members before and after external review of the document. Writing group members who had a significant (greater than $10 000) relationship with industry relevant to a recommendation were required to recuse themselves from voting on that recommendation.

### 1.3. Review and Approval (NEW)

The 2005 Guideline document was reviewed by 3 official reviewers nominated by the ACCF, 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: ACCF/AHA Committee to Develop Performance Measures for Heart Failure, ACCF/AHA Committee to Revise Guidelines for the Management of Patients With Acute Myocardial Infarction, ACCF/AHA/ESC Committee to Update Guidelines on the Management of Patients with Atrial Fibrillation, ACCF/AHA Committee to Update Guidelines on Coronary Artery Bypass Graft Surgery, ACCF 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 2009 focused update was reviewed by 2 external reviewers nominated by both the ACCF and AHA, as well as a reviewer from the ACCF/AHA Task Force on Practice Guidelines, 10 organizational reviewers representing the American College of Chest Physicians, the American College of Physicians, the American Academy of Family Physicians, the Heart Failure Society of America, and the International Society for Heart and Lung Transplantation, and 14 individual content reviewers. All information about reviewers' relationships with industry was collected and distributed to the writing committee and is published in this document (see Appendix 5 for details).

The 2009 focused update was approved for publication by the governing bodies of the ACCF and the AHA and endorsed by the International Society for Heart and Lung Transplantation.

### 1.4. Stages of Heart Failure (UPDATED)

The HF writing committee previously developed a new approach to the classification of HF (2), one that emphasized both the development and progression of the disease. In doing so, they 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 functional 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).

## 2. Characterization of Heart Failure as a Clinical Syndrome

### 2.1. Definition of Heart Failure

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

The clinical syndrome of HF may result from disorders of the pericardium, myocardium, endocardium, or great vessels, but the majority of patients with HF have symptoms due to an impairment of 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 (14). 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 (14). 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 Heart Failure (UPDATED)

*The changes in this section are made to clarify the role of functional assessment of the HF patient, beyond the NYHA functional classification, and to expand on the use of B-type natriuretic peptide (BNP) and N-terminal pro-B-type natriuretic peptide (NT-proBNP) testing within the context of the overall evaluation of the patient (Table 2).*

### Recommendations for Initial Clinical Assessment of Patients Presenting With Heart Failure

**CLASS I**

1. **A thorough history and physical examination should be obtained/performed in patients presenting with HF to identify cardiac and**

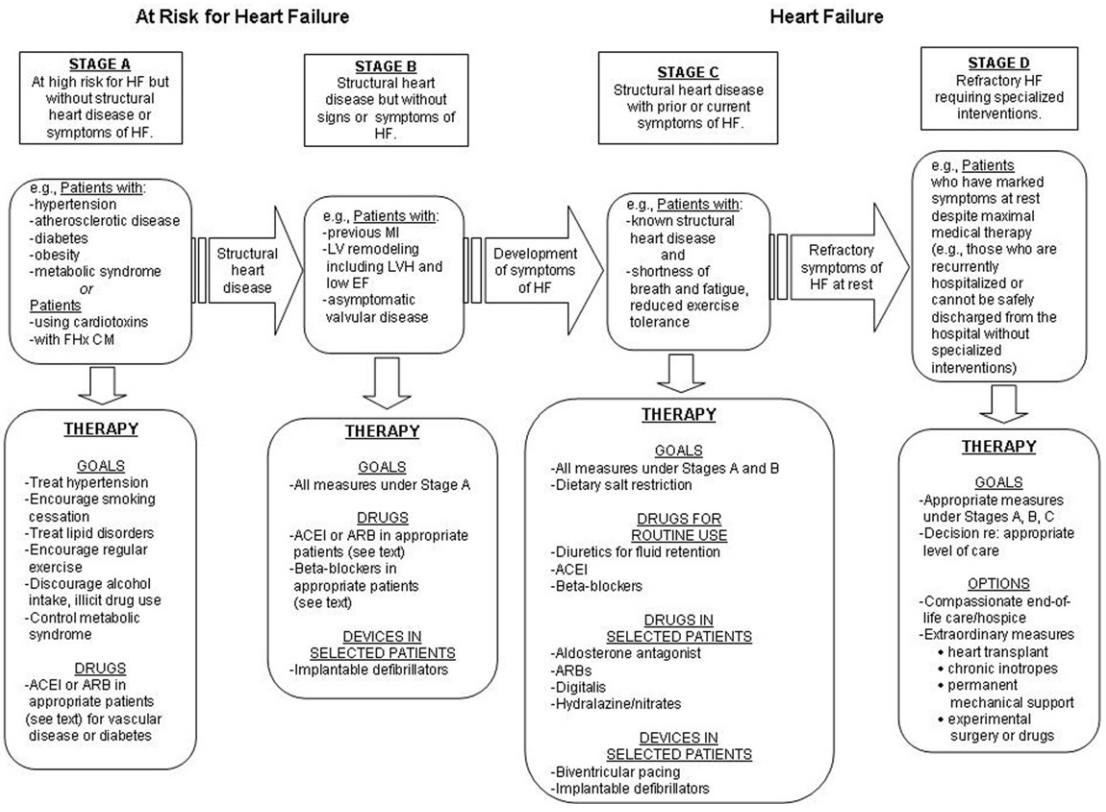


**Figure 1. Stages in the Development of Heart Failure/Recommended Therapy by Stage**

ACEI indicates angiotensin-converting enzyme inhibitor; ARB, angiotensin II receptor blocker; EF, ejection fraction; FHx CM, family history of cardiomyopathy; HF, heart failure; LV, left ventricular; LVH, left ventricular hypertrophy; and MI, myocardial infarction.

**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*)**
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 (posterior-anterior 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, left ventricular 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 (15–19). (*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 (20). (*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 (21–23). (*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 (24). (*Level of Evidence: C*)
9. Measurement of natriuretic peptides (BNP and NT-proBNP) can be useful in the evaluation of patients presenting in the urgent care setting in whom the clinical diagnosis of HF is uncertain. Measurement of natriuretic peptides (BNP and NT-proBNP) can be helpful in risk stratification (25–32). (*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 (24). (*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 Heart Failure

**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*)

**CLASS IIa**

1. Repeat measurement of EF and the severity of structural remodeling can be useful to provide 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**

1. 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 (UPDATED)

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 [33]).
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 myocardial infarction (MI), an arrhythmia, or a pulmonary or systemic thromboembolic event), patients may be found to have evidence of cardiac enlargement or dysfunction.

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 (34), 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.

### 3.1.2. Identification of a Structural and Functional Abnormality (UPDATED)

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 LV ejection fraction (EF) preserved or reduced? 2) Is the structure of the LV normal or abnormal? 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 (35). However, abnormalities can be present in any of these parameters in the absence of HF. No single parameter 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 EF, 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 (36).

Magnetic resonance imaging may also be used to identify myocardial viability and scar tissue (37). 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, LV hypertrophy, 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 Heart Failure

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

**Table 2. Evaluation of the Cause of Heart Failure—The History**

| History to include inquiry re: | Family history to include inquiry re: |
|---|---|
| Hypertension | Predisposition to atherosclerotic disease (history of MIs, strokes, PAD) |
| Diabetes | Sudden cardiac death |
| Dyslipidemia | Myopathy |
| Valvular heart disease | Conduction system disease (need for pacemaker) |
| Coronary or peripheral vascular disease | Tachyarrhythmia |
| Myopathy | Cardiomyopathy (unexplained HF) |
| Rheumatic fever | Skeletal myopathy |
| 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 | |

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

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 (38).

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 (39). 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 (UPDATED)

Laboratory testing may reveal the presence of disorders or conditions that can lead to or exacerbate HF. The initial evaluation of patients with HF should include a complete blood count, urinalysis, serum electrolytes (including calcium and magnesium), 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 reasonable and should be considered for all high-risk patients. However, other clinical signs of HIV infection typically precede any HF symptoms in those patients who develop HIV cardiomyopathy. 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 (see a recent review of the role of endomyocardial biopsy (24), and Section 3.1.3.4, Evaluation of the Possibility of Myocardial Disease. 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 natriuretic peptides (BNP and NT-proBNP). Several of the natriuretic peptides are synthesized by and released from the heart. Elevated plasma BNP levels have been associated with reduced LVEF (40), LV hypertrophy, 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.

Natriuretic peptides are sensitive to other biological factors, such as age, sex, weight, and renal function (41). Elevated levels lend support to a diagnosis of abnormal ventricular function or hemodynamics causing symptomatic HF (42). Trials with these diagnostic markers suggest use in the urgent-care setting, where they have been used in combination with clinical evaluation to differentiate dyspnea due to HF from dyspnea of other causes (15), and suggest that its use may reduce both the time to hospital discharge and the cost of treatment (43). BNP levels tend to be less

elevated in HF with preserved EF than in HF with low EF and are lower in obese patients (44,45). Levels of natriuretic peptides may be elevated meaningfully in women and in people over 60 years of age who do not have HF, and thus these levels should be interpreted cautiously in such individuals when distinguishing between cardiac and noncardiac causes of dyspnea. Elevated natriuretic peptide 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 (43,46).

#### 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 (47–49). 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 (15). 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 (16).

PATIENTS WITH CORONARY ARTERY DISEASE AND NO ANGINA. Controlled trials have not addressed the issue of whether coronary revascularization can improve clinical outcomes in patients with HF who do not have angina. Nevertheless, the ACC/AHA 2004 Guideline Update for Coronary Artery Bypass Graft Surgery (16) recommends revascularization in patients with a significant left main stenosis and in patients who have large areas of noninfarcted but hypoperfused and hypocontractile myocardium on noninvasive testing.

Observational studies have shown that revascularization can favorably affect 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 (50). 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 [51] and the ACC/AHA/ASNC Guidelines for Clinical Use of Cardiac Radionuclide Imaging [52]).

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 (16). 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 (17). 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 (53). 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 (54). 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 (55). 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 (56,57). 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 (58).

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

A variety of approaches have been used to quantify the degree of functional limitation imposed by HF. The most widely used scale is the NYHA functional classification (34), 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 assess-

ment 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 distension and its response to abdominal pressure, the presence and severity of organ congestion (pulmonary rales and hepatomegaly), and the magnitude of peripheral edema in the legs, abdomen, presacral area, and scrotum, as well as ascites in the abdomen.

The most reliable sign of volume overload is jugular venous distention (59–61). Right-sided filling pressures are elevated in the basal state or with abdominal compression (hepatojugular reflux) in many patients with chronically elevated elevated left-sided filling pressures (62). 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 $^{131}$I-tagged albumin have demonstrated plasma volume expansion in more than 50% of patients in whom clinical volume overload was not recognized (63). 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 (41).

### 3.2.3. Laboratory Assessment (UPDATED)

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 II 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 functional 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, Laboratory Testing) (42). Indeed, there is an increasing body of evidence demonstrating the power of the addition of BNP (or NT-proBNP) levels in the assessment of prognosis in a variety of cardiovascular disorders. 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 conclusively to improve outcomes more effectively than achievement of the target doses of drugs shown in clinical trials to prolong life (64). Ongoing trials will help to determine the role of serial BNP (or other natriuretic peptides) 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 (65).

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. Thus, it is appropriate to obtain a repeat EF after some period of optimal medical therapy, typically 4 to 6 months, to decide about the implantation of an implantable cardioverter-defibrillator (ICD). 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 (UPDATED)

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 (66). 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 (66,67). 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 (or NT-proBNP) 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 for management.

Because treatment of HF has improved over the past 10 years, the older prognostic models need to be revalidated (68), 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 (68). 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 ICDs (69).

## 4. Therapy

### 4.1. Patients at High Risk for Developing Heart Failure (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 hyperten-**

**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 | HF | 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 | — |
| Olmesartan | 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.

Asymptomatic CV Risk indicates reduction in future cardiovascular events; DN, diabetic nephropathy; H, hypertension; HF, heart failure; LVSD, asymptomatic left ventricular systolic dysfunction; and Post MI, reduction in heart failure or other cardiac events following myocardial infarction.

**sion with associated cardiovascular risk factors. (*Level of Evidence: C*)**

**CLASS III**

1. **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.

### 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 (70,71), and long-term treatment of both systolic and diastolic hypertension has been shown to reduce the risk of HF (72–74). A number of large, controlled studies have quite uniformly demonstrated that optimal blood pressure control decreases the risk of new HF by approximately 50% (75). Because approximately one fourth of the American population is hypertensive, and the lifetime risk of developing hypertension in the United States exceeds 75% (76), 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 (77). In the Framingham Heart Study, hypertension accounted for 39% of HF cases in men and 59% in women (70). 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 (73).

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 (78); target levels of blood pressure are lower in patients with associated major cardiovascular risk factors, especially those with diabetes mellitus (79,80). When an antihypertensive regimen is devised, optimal control of blood pressure should remain 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 (81). ACE inhibitors (ACEIs) and beta-blockers are also effective in the prevention of HF (78), whereas calcium antagonists and alpha-blockers are less effective in preventing HF syndrome (82). 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 (83,84), 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 (85) and irbesartan (86) 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 (87).

#### 4.1.1.2. TREATMENT OF DIABETES

Obesity and insulin resistance are important risk factors for the development of HF (88,89). The presence of clinical diabetes mellitus markedly increases the likelihood of HF in patients without structural heart disease (90) and adversely affects the outcomes of patients with established HF (91,92). 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 (93). 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 (70). 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 (83,94). Long-term treatment with several ACEIs or ARBs has been shown to decrease the risk of renal disease in diabetic patients (95,96), and prolonged therapy with the ACEI ramipril has been shown to lower the likelihood of cardiovascular death, MI, and HF (83). 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 (85,86,97).

#### 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 (98). The major adverse consequence of the metabolic syndrome is cardiovascular disease in general and may include an increased incidence of new HF (99). As noted previously, the appropriate treatment of hypertension, diabetes mellitus, and dyslipidemia (100) 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 (87). In one large-scale trial, long-term treatment with an ACEI decreased the risk of the primary endpoint 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 endpoint, although it was improved (83). 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 primary nor a secondary endpoint (84). 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 (101). 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 (100,102–104).

#### 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 (105,106). 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 (107) and chemotherapeutic agents such as anthracyclines, immunotherapy such as trastuzumab, or high-dose cyclophosphamide (108–110). 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 (111).

#### 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 (112). 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 (113). 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) (114,115). 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 Heart Failure 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/ACP-ASIM Guidelines for the Management of Patients With Chronic Stable Angina [712]). (*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**

1. **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 (116,117). 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 HF after MI that has already been treated

with ACEIs and beta blockers (118,119). Other preventive measures have been addressed in related guidelines (120).

### 4.2.1. Prevention of Cardiovascular Events

#### 4.2.1.1. PATIENTS WITH AN ACUTE MYOCARDIAL INFARCTION

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 (121), and these interventions can reduce the risk of death, especially in patients with a prior myocardial injury (122,123). 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 (124–130). Combined neurohormonal blockade (beta blocker and ACEI or ARB) produces additive benefits (131). For recommendations on the treatment of patients with MI, see the ACC/AHA Guidelines for the Management of Patients With ST-Elevation Myocardial Infarction (11).

#### 4.2.1.2. PATIENTS WITH A HISTORY OF MI BUT NORMAL LEFT VENTRICULAR EJECTION FRACTION

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 (72,73). Patients with a recent MI should also receive treatment with ACEIs and beta blockers (124,125,128,129,131), 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 (83,84).

#### 4.2.1.3. PATIENTS WITH HYPERTENSION AND LEFT VENTRICULAR HYPERTROPHY

See Section 4.1.1.1.

#### 4.2.1.4. PATIENTS WITH CHRONIC REDUCTION OF LEFT VENTRICULAR EJECTION FRACTION 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 nonischemic cardiomyopathy (117,132). 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 (127,131). 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 nonischemic cardiomyopathy have not included functional class I patients and the efficacy of ICDs in this population as a whole is unknown (133). 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 (134), 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 (135).

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 (136,137). 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, Treatment of Special Populations).

#### 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 (138–141). 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 (142,143) have suggested that pro-

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

| Drug | Initial Daily Dose(s) | Maximum Total Daily Dose | Duration of Action |
|---|---|---|---|
| Loop Diuretics | | | |
| Bumetanide | 0.5 to 1.0 mg once or twice | 10 mg | 4 to 6 hours |
| Furosemide | 20 to 40 mg once or twice | 600 mg | 6 to 8 hours |
| Torsemide | 10 to 20 mg once | 200 mg | 12 to 16 hours |
| Thiazide Diuretics | | | |
| Chlorothiazide | 250 to 500 mg once or twice | 1000 mg | 6 to 12 hours |
| Chlorthalidone | 12.5 to 25 mg once | 100 mg | 24 to 72 hours |
| Hydrochlorothiazide | 25 mg once or twice | 200 mg | 6 to 12 hours |
| Indapamide | 2.5 mg 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 |
| Spironolactone | 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 | | |

*Eplerenone, although also a diuretic, is primarily used in chronic heart failure as a suppressor of the rennin-angiotensin-aldosterone system. †Higher doses may occasionally be used with close monitoring.
IV indicates intravenous; and mg, milligrams.

longed therapy with hydralazine and nifedipine in patients with severe aortic regurgitation and preserved LV function might act to minimize structural changes in the ventricle and thereby possibly delay the need for surgical intervention; however, these drugs are often poorly tolerated in this setting, and no trial has shown that these vasodilators can reduce the risk of HF or death (see ACC/AHA Guidelines for the Management of Patients With Valvular Heart Disease [138]). There are no long-term studies of vasodilator therapy in patients with severe asymptomatic mitral regurgitation.

### 4.2.2. Early Detection of Heart Failure

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 Left Ventricular Ejection Fraction (UPDATED)

*Changes in this section focused on 3 areas: recommendations about electrical device therapy (e.g., cardiac resynchronization therapy [CRT] and ICDs), the use of a fixed dose combination of hydralazine and isosorbide dinitrate in self-identified African Americans, and the management of atrial fibrillation in patients with HF. The previous version of the guidelines had a number of possibly confusing recommendations about selection of patients for ICD implantation. The writing group has tried to simplify the recommendations, and keep them concordant with the most recent guidelines covering the same issue (69,144). Updated trial information has led to the change in the recommendations about the use of hydralazine/isosorbide dinitrate and about the management of atrial fibrillation (Table 3).*

#### 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) (145–157). (*Level of Evidence: A*)**
4. **Use of 1 of the 3 beta blockers proven to reduce mortality (i.e., bisoprolol, carvedilol, and sustained release metoprolol succinate) is recommended for all stable patients with current or prior symptoms of HF and reduced LVEF, unless contraindicated (see Table 3) (158–176). (*Level of Evidence: A*)**
5. **Angiotensin II receptor blockers (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) (130,177–186). (*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 drugs, most antiarrhythmic drugs, and most calcium channel blocking drugs; see text) (187–193). (*Level of Evidence: B*)
7. 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 (193a–193d). (*Level of Evidence: B*)
8. 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 (194–196). (*Level of Evidence: A*)
9. Implantable cardioverter-defibrillator therapy is recommended for primary prevention of sudden cardiac death to reduce total mortality in patients with non-ischemic dilated cardiomyopathy or ischemic heart disease at least 40 days post-MI, a LVEF less than or equal to 35%, and NYHA functional class II or III symptoms while receiving chronic optimal medical therapy, and who have reasonable expectation of survival with a good functional status for more than 1 year (144,196–202). (*Level of Evidence: A*)
10. Patients with LVEF of less than or equal to 35%, sinus rhythm, and NYHA functional class III ambulatory class IV symptoms despite recommended optimal medical therapy and who have cardiac dyssynchrony, which is currently defined as a QRS duration greater than or equal to 0.12 seconds, should receive cardiac resynchronization therapy, with or without an ICD, unless contraindicated (203–218). (*Level of Evidence: A*)
11. Addition of an aldosterone antagonist is recommended 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 2.5 mg per dL or less in men or 2.0 mg per dL or less in women and potassium should be less than 5.0 mEq per liter. Under circumstances where monitoring for hyperkalemia or renal dysfunction is not anticipated to be feasible, the risks may outweigh the benefits of aldosterone antagonists (219–221). (*Level of Evidence: B*)
12. The combination of hydralazine and nitrates is recommended to improve outcomes for patients self-described as African-Americans, with moderate-severe symptoms on optimal therapy with ACEIs, beta blockers, and diuretics (222,223). (*Level of Evidence: B*)

#### CLASS IIa

1. It is reasonable to treat patients with atrial fibrillation and HF with a strategy to maintain sinus rhythm or with a strategy to control ventricular rate alone (224–228). (*Level of Evidence: A*)
2. Maximal exercise testing with or without measurement of respiratory gas exchange is reasonable to facilitate prescription of an appropriate exercise program for patients presenting with HF. (*Level of Evidence: C*)
3. 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 (130,177–185). (*Level of Evidence: A*)
4. Digitalis can be beneficial in patients with current or prior symptoms of HF and reduced LVEF to decrease hospitalizations for HF (134,229–235). (*Level of Evidence: B*)
5. 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 (222,236). (*Level of Evidence: B*)
6. For patients who have LVEF less than or equal to 35%, a QRS duration of greater than or equal to 0.12 seconds, and atrial fibrillation (AF), CRT with or without an ICD is reasonable for the treatment of NYHA functional class III or ambulatory class IV heart failure symptoms on optimal recommended medical therapy (2, 237). (*Level of Evidence: B*)
7. For patients with LVEF of less than or equal to 35% with NYHA functional class III or ambulatory class IV symptoms who are receiving optimal recommended medical therapy and who have frequent dependence on ventricular pacing, CRT is reasonable (2). (*Level of Evidence: C*)

#### 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 (222,238,239). (*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 (130,177–185). (*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 (135,240–242). (*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 (UPDATED)

Measures listed as Class I recommendations for patients in stage A or B are also appropriate for patients with current or prior symptoms of HF (also see Section 5, Treatment of Special Populations). 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 (243–246).

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

1) Antiarrhythmic agents (247) can exert important cardiodepressant and proarrhythmic effects. Of available agents, only amiodarone and dofetilide (248) 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 (249). Of available calcium channel blockers, only the vasoselective ones have been shown not to adversely affect survival (240,250).
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 (187–190). 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, Angiotensin Converting Enzyme Inhibitors in the Management of Heart Failure).

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 (251). Activation of both the sympathetic nervous system and renin-angiotensin system can lead to hypokalemia (252,253), and most drugs used for the treatment of HF can alter serum potassium (254). Even modest decreases in serum potassium can increase the risks of using digitalis and antiarrhythmic drugs (251,255), and even modest increases in serum potassium may prevent the use of treatments known to prolong life (256). Hence, many experts believe that serum potassium concentrations should be targeted in the 4.0 to 5.0 mEq per liter range. In some patients, correction of potassium deficits may require supplementation of magnesium and potassium (257). 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 used is close observation and follow-up. Nonadherence with diet and medications can rapidly and profoundly affect the clinical status of patients, and increases in body weight and minor changes in symptoms commonly precede by several days the occurrence of major clinical episodes that require emergency care or hospitalization. Patient education and close supervision, which includes surveillance by the patient and his or her family, can reduce the likelihood of nonadherence and lead to the detection of changes in body weight or clinical status early enough to allow the patient or a healthcare provider an opportunity to institute treatments that can prevent clinical deterioration. Supervision need not be performed by a physician and may ideally be accomplished by a nurse or physician's assistant with special training in the care of patients with HF. Such an approach has been reported to have significant clinical benefits (258–261).

*Recommendations Concerning Aldosterone Antagonists.* The addition of low-dose aldosterone antagonists is recommended 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 (118,256). 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 have 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 (Candesartan in Heart Failure: Assessment of Reduction in Mortality and Morbidity) add-on trial (186) 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.

#### 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 (262). 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 (263,264). 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 (265,266). 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 (267–269). 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 (270,271).
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 (121,123), 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 (269).
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 (269). The risk of clinical decompensation can be reduced, however, when diuretics are combined with an ACEI and a beta blocker (229).
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 (272).

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 (272,273) and the risk of renal insufficiency with ACEIs and ARBs (274). 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 (275,276). 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 (277).

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 making 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 (278–280). 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) (188,189,281), or have a significant impairment of renal function or perfusion (275). Diuretic resistance can generally be overcome by the intravenous administration of diuretics (including the use of continuous infusions) (282), the use of 2 or more diuretics in combination (e.g., furosemide and metolazone) (283–286), or the use of diuretics together with drugs that increase renal blood flow (e.g., positive inotropic agents) (286).

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 (287). 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 (264). Potassium deficits can be corrected by the short-term use of potassium supplements or, if severe, by the addition of magnesium supplements (288). 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 (272–274,289), 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

**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 | |
| Metozalone (as Zaroxolyn or Diulo) | 2.5 to 5 mg PO once or twice daily with loop diuretic | |
| IV 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 | |

IV indicates intravenous; kg, kilograms; mg, milligrams; and PO, by mouth.

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 in the Management of Heart Failure.* 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 (290–292). In experimental models of HF, ACEIs modify cardiac remodeling more favorably than ARBs (293–296), and this advantage of ACEIs is abolished by the coadministration of a kinin receptor blocker (293,295). Angiotensin converting enzyme inhibitors have been evaluated in more than 7000 patients with HF who participated in more than 30 placebo-controlled clinical trials (146). 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 (145,147–157). In addition, ACEIs can reduce the risk of death and the combined risk of death or hospitalization (155–157). 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 ACEIS. *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 prescribed without diuretics in patients with a current or recent history of fluid retention, because diuretics are needed to maintain sodium balance and prevent the development of peripheral and pulmonary edema (269). Angiotensin converting enzyme inhibitors are often preferred over ARBs or direct-acting vasodilators (156,297) 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 mEq 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 ACEIS. *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 (146). Although some have suggested that drugs in this class may differ in their ability to inhibit tissue ACE, no trial has shown that tissue ACE inhibiting agents are superior to other ACEIs in any clinical aspect of HF. Nevertheless, in selecting among ACEIs, it is recommended that preference be given to ACEIs that have been shown to reduce morbidity and mortality in clinical trials in HF or post-MI populations (captopril, enalapril, lisinopril, perindopril, ramipril, and trandolapril), because these studies have clearly defined a dose that is effective in modifying the natural history of the disease. Such information is generally lacking for ACEIs that have not been shown to be effective in large-scale studies.

Treatment with an ACEI should be initiated at low doses (see Table 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 preexisting 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 (274,277), 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 (155–157).

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 (298,299). 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 (145,270). 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 (300) 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 (274,277). 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 (190,252).

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 (301,302). 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 (303,304), an effect not seen with nonaspirin antiplatelet agents (e.g., clopidogrel) (305).

In several multicenter trials, concomitant use of aspirin was associated with a diminution of the effect of ACEIs on survival and on cardiovascular morbidity (306,307). A recent comprehensive systematic overview of 22 060 patients from 6 long-term randomized trials of ACEIs reevaluated 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 (308). A second retrospective review subsequently also reported no adverse effect of concomitant aspirin use with ACEIs on long-term survival (309). 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 (310,311), 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 (312). 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 ACEIS. *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 hypovo-

lemia, a recent marked diuresis, or severe hyponatremia (serum sodium concentration less than 130 mmol per liter) (313).

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 longterm 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 (314), and ACE inhibition may cause functional renal insufficiency (274). 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 hyponatremic patients) (315). 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 (316), but in only 5% to 15% of patients with mild to moderate symptoms (317). The risks are substantially greater if patients have bilateral renal artery stenosis or are taking nonsteroidal anti-inflammatory drugs (189,252,318). 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 (274). 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 (319).

*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 (320); the frequency of cough is approximately 5% to 10% in white patients of European descent and rises to nearly 50% in Chinese patients (321). It is characteristically nonproductive, is accompanied by a persistent and annoying "tickle" in the back of the throat, usually appears within the first months of therapy, disappears within 1 to 2 weeks of discontinuing treatment, and recurs within days of rechallenge. Other causes of cough, especially pulmonary congestion, should always be considered, and the ACEI should be implicated only after these have been excluded. Demonstration that the cough disappears after drug withdrawal and recurs after rechallenge with another ACEI strongly suggests that ACE inhibition is the cause of the cough. In a number of studies of ACEI cough, it was found that this symptom did not recur with rechallenge and probably was a coincidental finding. Because of the long-term benefits of ACEIs, physicians should encourage patients to continue taking these drugs if the cough is not severe. Only if the cough proves to be persistent and troublesome should the physician consider withdrawal of the ACEI and the use of alternative medications (e.g., an ARB).

2. ANGIOEDEMA

Angioedema occurs in fewer than 1% of patents 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 (320). 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 (177,322–324).

**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 inhibition of kininase would produce all of the benefits of ACEIs while minimizing the risk of their adverse reactions (325). However, it is now known that some of the benefits may be related to the accumulation of kinins (326) 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 (293–295). 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-

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

| Drug | Initial Daily Dose(s) | Maximum Doses(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 | | |
| Spironolactone | 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<br>50 mg twice for patients >85 kg |
| Metoprolol succinate extended release (metoprolol CR/XL) | 12.5 to 25 mg once | 200 mg once |

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

controlled studies, long-term therapy with ARBs produced hemodynamic, neurohormonal, and clinical effects consistent with those expected after interference with the renin angiotensin system (178–183). 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 (130). 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 (177,184) 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 (185). 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 (184,185,327).

*Recommendations Concerning Angiotensin Receptor Blockers.* Angiotensin converting enzyme inhibitors remain the first choice for inhibition of the renin-angiotensin system in chronic HF, but ARBs can now be considered a reasonable alternative. Candesartan improved outcomes in patients with preserved LVEF who were intolerant of ACEIs in the Candesartan in Heart Failure Assessment of Reduction in Mortality and Morbidity (CHARM) Alternative trial (177). 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 (177). 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 (328). 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 (329–335).

Spironolactone is the most widely used aldosterone antagonist. In a large-scale, long-term trial (256), low doses of spironolactone (starting at 12.5 mg daily) were added to ACEI therapy for patients with NYHA functional 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.

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**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/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 minute 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 of 12.5 mg or eplerenone 25 mg is recommended, following 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. Non-steroidal anti-inflammatory drugs and cyclo-oxygenase-2 inhibitors should be avoided.
6. Potassium supplements should be discontinued or reduced.
7. Close monitoring of serum potassium is required; potassium levels and renal function should be checked in 3 days and at 1 week after initiating therapy and at least monthly for the first 3 months.
8. Diarrhea or other causes of dehydration should be addressed emergently.

*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 (335a) 95% of patients had creatinine less than or equal to 1.7 mg per dL.

ACEI indicates angiotensin converting enzyme inhibitor.

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 minute (118).

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 minute 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.

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 (219), in which half of the subjects with hyperkalemia had potassium levels in excess of 6 mEq per liter. Similar results were reported from Norway (221). 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 (220). 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 (118).

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 (118) 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 (336) and by impairing sodium excretion by the kidneys (337). 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 (316,338,339). 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 (253,340–342). 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 (343). These deleterious effects are mediated through actions on alpha-1–, beta-1–, and beta-2–adrenergic receptors (253,316,336–343).

Three beta blockers have been shown to be effective in reducing the risk of death in patients with chronic HF: bisoprolol (158) and sustained-release metoprolol (succinate) (159), which selectively block beta-1–receptors, and carvedilol (165,166), 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 (160,161,344). 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 (160). In one trial (161), 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 (159) that showed that sustained-release metoprolol (metoprolol succinate) reduces the risk of death (162). 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 (89,93,158,162–164,166,167,345). 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 functional 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 (345).

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 (168–175). In addition, like ACEIs, beta blockers can reduce the risk of death and the combined risk of death or hospitalization (158,162,164,176,346). 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 (158,162,164,175,176).

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 (298,347). 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 (348–350).

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 uptitration period. In addition, because initiation of therapy with a beta-blocker can cause fluid alpha retention (348–350), 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 (158,162,164,165). 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 (351).

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 (273). 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 (352).

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 (353). 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 (348–350), 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 (354). 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 (164). 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 (348–350). 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 (Na+-K+) adenosine triphosphatase (ATPase) (355). 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 Na+-K+ ATPase in vagal afferent fibers acts to sensitize cardiac baroreceptors, which in turn reduces sympathetic outflow from the central nervous system (356,357). In addition, by inhibiting Na+-K+ ATPase in the kidney, digitalis reduces the renal tubular reabsorption of sodium (358); the resulting increase in the delivery of sodium to the distal tubules leads to the suppression of renin secretion from the kidneys (359). 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 (360). 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 (229–235). 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 (134).

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 (361,362). Digoxin may also be added to the initial regimen in patients with severe symptoms who have not yet responded symptomat-

ically 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 (363–366). 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 (367). 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 (368). In a retrospective analysis of the Digitalis Investigation Group trial, risk-adjusted mortality increased as the plasma concentrations exceeded 1.0 ng per mL (369). 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 (370). The principal adverse reactions occur primarily when digoxin is administered in large doses, but large doses may not be needed to produce clinical benefits (371–373). 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 (374,375). 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 (219,376,377). The dose of digoxin should be reduced if treatment with these drugs is initiated. Spironolactone does not inhibit the disposition of digoxin (378); 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 (379).

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 (134). 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 (380). Digoxin should be used with caution or not used at all in post-MI patients, particularly if they have ongoing ischemia (381).

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 (UPDATED).** Patients with LV dilation and reduced LVEF frequently manifest ventricular tachyarrhythmias, both nonsustained ventricular tachycardia (VT) and sustained VT. The cardiac mortality of patients with all types of ventricular tachyarrhythmias is high. The high mortality results from progressive HF, as well as from sudden death. Sudden death 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 (382), 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 (383).

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 (124,125,158,162,164). Aldosterone antagonists decrease sudden death and overall mortality in HF early after MI and in advanced HF (118). Sudden unexpected death can be decreased further by the use of implanted devices that terminate sustained arrhythmias (144,205). 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 should be recommended in all patients who have had a life-threatening tachyarrhythmia and have an 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 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 (198). 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 (384–386). Antiarrhythmic drugs to suppress premature ventricular depolarizations and nonsustained ventricular arrhythmias have not improved survival (191,192), 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 (193,247,

387). This risk is especially high with the use of Class IA agents (quinidine and procainamide), Class IC agents (flecainide and propafenone), and some Class III agents (d-sotalol) (191,192,388,389), which have increased mortality in post-MI trials (390).

Amiodarone is a Class III antiarrhythmic agent but differs from other drugs in this Class in having a sympatholytic effect on the heart (391). Amiodarone has been associated with overall neutral effects on survival when administered to patients with low EF and HF (196,392–394). 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 (393,394). 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 (199).

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 (196,200,201). The first of these demonstrated that ICDs, compared with standard medical therapy, decreased the occurrence of total mortality for patients with EF of 30% or less after remote MI (200). 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 (201). A third trial examining the benefit of ICD implantation for patients with EF less than 35% and NYHA functional 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 bpm. This represented a relative mortality decrease of 23%, which was a survival increase of 11% (196). 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 DEFINITE (Defibrillators in Non-Ischemic Cardiomyopathy Treatment Evaluation) trial compared medical therapy alone with medical therapy plus an ICD in patients with nonischemic cardiomyopathy, NYHA functional class I to III HF, and an LVEF less than 36% (395). 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 MADIT II (Multicenter Automatic Defibrillator Implantation II) (200) and the SCD-HeFT (Sudden Cardiac Death in Heart Failure: Trial of prophylactic amiodarone versus implantable defibrillator therapy) (196).

There is an intrinsic variability in measurement of EF particularly shortly after recovery from an acute coronary syndrome event. Moreover, as reviewed earlier, the pivotal primary prevention trials used a variable inclusion EF, ranging below 30% or 36%. Given the totality of the data demonstrating the efficacy of an ICD in reducing overall mortality in a population with dilated cardiomyopathy of either ischemic or nonischemic origins, the current recommendation is to include all such patients with an LVEF of less than or equal to 35%.

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 (396).

It is important to recognize that ICDs have the potential to aggravate HF and have been associated with an increase in HF hospitalizations (200,202). 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/HRS 2008 Guidelines for Device-Based Therapy of Cardiac Rhythm Abnormalities (144) 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 (196,200). 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 or equal to 35% 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. 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 important, the possible reasons and process for potential future deactivation of defibrillator features should be discussed 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 (397). 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 (398,399) and may thereby attenuate the process of ventricular remodeling (400) 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 (239) 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 (401,402). In addition to its direct vascular actions, hydralazine in theory may interfere with the biochemical and molecular mechanisms responsible for the progression of HF (403,404) and the development of nitrate tolerance (405–408). There are limited data regarding the use of hydralazine alone in HF.

**4.3.1.3.3.** HYDRALAZINE AND ISOSORBIDE DINITRATE (UPDATED). 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 (238,239). However, in another large-scale trial that compared the vasodilator combination with an ACEI, the ACEI produced more favorable effects on survival (156), 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 African American cohort (222). A confirmatory trial has been done. In that trial, which was limited to the patients self-described as African American, 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 (223). The benefit was presumed to be related to enhanced nitric oxide bioavailability. Accordingly, this combination is recommended for African Americans who remain symptomatic despite optimal medical therapy. 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 ACEI 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 (156,238). For patients with more severe HF 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 (UPDATED). Approximately one-third of patients with low EF and class III to IV symptoms of HF manifest a QRS duration greater than 0.12 seconds (409–411). 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 (412–414). Ventricular dyssynchrony has also been associated with increased mortality in HF patients (206–208). Dyssynchronous contraction can be addressed by electrically activating the right and left ventricles in a synchronized manner with a biventricular pacemaker device. This approach to HF therapy, commonly called cardiac resynchronization therapy (CRT), may enhance ventricular contraction and reduce the degree of secondary mitral regurgitation (209–211). In addition, the short-term use of CRT has been associated with improvements in cardiac function and hemodynamics without an accompanying increase in oxygen use (212), as well as adaptive changes in the biochemistry of the failing heart (210).

To date, more than 4000 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. CRT, 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 (213) or to the combination of CRT and ICD (205,214,215). In a meta-analysis of several CRT trials, HF hospitalizations were reduced by 32% and all-cause mortality by 25% (215). The effect on mortality in this meta-analysis became apparent after approximately 3 months of therapy (215). In 1 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% (216). 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% (204). 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 longer than 0.12 seconds, the average QRS duration in the large trials was longer than 0.15 seconds, with less information demonstrating benefit in patients with lesser prolongation of QRS. Two small studies, one randomized (217) and the other observational (218), 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. 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 published studies have addressed this situation as yet. Recommendations regarding CRT for patients with LVEF of less than or equal to 35%, NYHA functional class III, and ambulatory class IV symptoms or dependence on ventricular

pacing have been updated to be consistent with the ACC/AHA/HRS 2008 Guidelines for Device-Based Therapy of Cardiac Rhythm Abnormalities (144).

Ten studies have reported on CRT peri-implant morbidity and mortality. There were 13 deaths in 3113 patients (0.4%). From a pooled assessment of 3475 patients in 17 studies, the success rate of implantation was approximately 90% (215). 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 (215).

**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 (415) and in the belief that physical activity might accelerate the progression of LV dysfunction (416–418); 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 (243,246). Limitations of activity not only may impair exercise capacity but also may produce adverse psychological effects and impair peripheral vasodilatory responses (245,419). These findings have led to the hypothesis that exercise training might improve the clinical status of patients with chronic HF (243,420).

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 (421–430). The improvement was comparable to that achieved with pharmacological interventions (420), was in addition to the benefits of ACEIs and beta blockers (422,423), and was associated with an enhancement of endothelium-dependent peripheral vasodilation and skeletal muscle metabolism (422,431). 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 (429).

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 (424,432,433). In the experimental setting, exercise appears to attenuate the rate of progression of HF (434,435). 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 (430), 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 (436). 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 (437). 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 (438,439). 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 (440). 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 (441). External counterpulsation has been shown to reduce the frequency and severity of anginal attacks in patients with symptomatic coronary artery disease (442). A possible mechanism of action for this observed clinical effect may be an improvement in endothelial function of the coronary vascular bed (443,444). Early trials of this therapy in patients with HF and low EF have been encouraging, and a randomized trial has been completed recently (445,446). 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 V1A receptor, which is found on vascular smooth muscle cells and in the myocardium, and the V2 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 (447).

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 (448,449). Currently, longer-term clinical trials are under way to determine the role, if any, of these vasopressin antagonists in patients with chronic HF (450,451).

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 (452,453).

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 (454). Clinical trials in Europe (455) 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 (456–458). 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 (459–461). 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 (462,463).

They are currently under investigation as adjunctive therapy, administered on an intermittent outpatient basis, for advanced chronic 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 (464–469). Aside from replenishment of documented deficiencies, randomized trials have failed to demonstrate benefit for routine vitamin, nutritional, or hormonal supplementation (470).

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 (471–474). 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 Integrating Complementary Medicine Into Cardiovascular Medicine (475) will provide more details regarding cardiovascular issues with alternative and complementary medicine.

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).

4.3.1.5.2. INTERMITTENT INTRAVENOUS POSITIVE INOTROPIC THERAPY (UPDATED). Although positive inotropic agents can improve cardiac performance during short- and long-term therapy (476,477), long-term oral therapy with these drugs has not improved symptoms or clinical status (233,478–488) and has been associated with a significant increase in mortality, especially in patients with advanced HF (486,489–494). 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 (59–61).

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 (59–61,495). 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 1 placebo-controlled trial of intermittent intravenous positive inotropic therapy has been published (496), 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.

Given the lack of evidence to support their efficacy and concerns about their toxicity, intermittent infusions of positive inotropic agents (whether at home, in an outpatient clinic, or in a short-stay unit) should not be used 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 (226,227).

### 4.3.2. Patients With Heart Failure and Normal Left Ventricular Ejection Fraction

#### 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**

1. **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.

**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 |
| Physicians might recommend coronary revascularization 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 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 might be considered. | IIb | C |

#### 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 (497), and a large, randomized study that enrolled patients with HF and normal EF has been completed (327). Currently, a number of investigators are seeking to clarify the epidemiology, clinical characteristics, and prognosis of patients with HF and a normal LVEF (498).

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 (499–503). Some investigators have found that in a significant number of patients, a tendency to fluid retention and reduced vascular compliance, rather than myocardial stiffness, represent the principal abnormalities (504). 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 (497). 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 (500). This observation may be related to the fact that aging has a greater impact on ventricular filling characteristics than on EF (505). 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 (506).

A number of recent investigations have focused on the differences between HF with preserved EF and that with low LVEF (48,49,498). Myocardial infarction or other evidence of atherosclerotic disease appears to be less common in HF with normal LVEF, but hypertension is at least as common in this subgroup. The morbidity and mortality associated with HF and a relatively preserved LVEF may be nearly as profound as that with low LVEF; frequent and repeated hospitalizations characterize the patient with HF and a normal LVEF (507,508). 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

**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.

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 (509–512). 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 (503,513) (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 (514–520). The analysis of BNP levels in association with echocardiographic filling patterns can improve diagnostic accuracy. For example, a normal BNP level along with completely normal diastolic end-filling parameters makes HF much less likely; however, HF does remain a strictly clinical diagnosis (521).

#### 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 (134,241,522–524). 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 (327). 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 endpoint.

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 (503). 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 (497). 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 (525), 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 (78). 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) (78,524,526). 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 [16]).

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 Heart Failure (Stage D) (UPDATED)

*The role of intermittent infusions as effective treatment for advanced HF has been further clarified by an additional multicenter trial (Table 4).*

### Recommendations

**CLASS I**

1. **Meticulous identification and control of fluid retention is recommended in patients with refractory end-stage HF (279,282,527–532). (*Level of Evidence: B*)**
2. **Referral for cardiac transplantation in potentially eligible patients is recommended for patients with refractory end-stage HF (533). (*Level of Evidence: B*)**
3. **Referral of patients with refractory end-stage HF to a HF program with expertise in the management of refractory HF is useful (534–537). (*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 the defibrillator. (*Level of Evidence: C*)**

**CLASS IIa**

1. **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 (538,539). (*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 (533,540). (*Level of Evidence: C*)**
2. **The effectiveness of mitral valve repair or replacement is not well established for severe secondary mitral regurgitation in refractory end-stage HF (141 541,542). (*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 (543,544). (*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 vasoactive and positive inotropic agents are not recommended for patients with refractory end-stage HF (545,546). (*Level of Evidence: A*)**

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 (see also 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 (263,275). 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) (283,285). If the patient continues to exhibit evidence of volume overload despite these measures, hospitalization is generally required for further adjustment of therapy (282,527), 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 (547,548). The use of such mechanical methods of fluid removal can produce meaningful clinical bene fits 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 (549), because unresolved edema may itself attenuate the response to diuretics (278–280). 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 (258–261).

### 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 (155,158,162–165,297,298,300–302,305,310–321,336–343,550). 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 (174,551).

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 (238), 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 (256); 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 (325) 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 (297,552).

### 4.4.3. Intravenous Peripheral Vasodilators and Positive Inotropic Agents (UPDATED)

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 (540). 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 (352,553). 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 (554).

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 may provide palliation of symptoms as part of an overall plan to allow the patient to die with comfort at home (543,544). 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 (536). Intermittent outpatient infusions of either vasoactive drugs such as nesiritide or positive inotropic drugs have not shown to improve symptoms or survival in patients with advanced HF (536,545,546).

### 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 (555,556). 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 (557).

Alternative 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 (141). 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 nonrandomized series of patients considered appropriate candidates for mitral valve repair did not demonstrate a survival advantage (541).

Although both cardiomyoplasty and left ventriculectomy (Batista procedure) at one time generated considerable excitement as potential surgical approaches to the treatment of refractory HF (558,559), these procedures failed to result in clinical improvement and were associated with a high risk of death (560). A variant of the aneurysmectomy procedure is now being developed for the management of patients with ischemic cardiomyopathy (458), but its role in the management of HF remains to be defined. None of the current surgical reconstruction techniques offer "rescue therapy" to patients with critical hemodynamic compromise.

**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 minute with achievement of anaerobic metabolism |
| Severe symptoms of ischemia that consistently limit routine activity and are not amenable to coronary artery bypass surgery or percutaneous coronary intervention |
| Recurrent symptomatic ventricular arrhythmias refractory to all therapeutic modalities |
| **Relative Indications** |
| Peak $VO_2$ 11 to 14 mL per kg per minute (or 55% predicted) and major limitation of the patient's daily activities |
| Recurrent unstable ischemia not amenable to other intervention |
| Recurrent instability of fluid balance/renal function not due to patient noncompliance with medical regimen |
| **Insufficient Indications** |
| Low left ventricular ejection fraction |
| History of functional class III or IV symptoms of HF |
| Peak $VO_2$ greater than 15 mL per kg per minute (and greater than 55% predicted) without other indications |

HF indicates heart failure; IV, intravenous; and $VO_2$, oxygen consumption per unit time.

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 (561). 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 (562). 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 (563). 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 (564), 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.

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.

## 4.5. The Hospitalized Patient (NEW)

### Recommendations

**CLASS I**

1. The diagnosis of HF is primarily based on signs and symptoms derived from a thorough history and physical examination. Clinicians should determine the following:
   a. adequacy of systemic perfusion;
   b. volume status;
   c. the contribution of precipitating factors and/or comorbidities;
   d. if the heart failure is new onset or an exacerbation of chronic disease; and
   e. whether it is associated with preserved ejection fraction.

   Chest radiographs, electrocardiogram, and echocardiography are key tests in this assessment. (*Level of Evidence: C*)
2. Concentrations of B-type natriuretic peptide (BNP) or N-terminal pro-B-type natriuretic peptide (NT-proBNP) should be measured in patients being evaluated for dyspnea in which the contribution of HF is not known. Final diagnosis requires interpreting these results in the context of all available clinical data and ought not to be considered a stand-alone test (565,566). (*Level of Evidence: A*)
3. Acute coronary syndrome precipitating HF hospitalization should be promptly identified by electrocardiogram and cardiac troponin testing, and treated as appropriate to the overall condition and prognosis of the patient. (*Level of Evidence: C*)
4. It is recommended that the following common potential precipitating factors for acute HF be identified as recognition of these comorbidities is critical to guide therapy:
   a. acute coronary syndromes/coronary ischemia;
   b. severe hypertension;
   c. atrial and ventricular arrhythmias;
   d. infections;
   e. pulmonary emboli;
   f. renal failure; and
   g. medical or dietary noncompliance. (*Level of Evidence: C*)
5. Oxygen therapy should be administered to relieve symptoms related to hypoxemia. (*Level of Evidence: C*)
6. Whether the diagnosis of HF is new or chronic, patients who present with rapid decompensation and hypoperfusion associated with decreasing urine output and other manifestations of shock are critically ill and rapid intervention should be used to improve systemic perfusion. (*Level of Evidence: C*)
7. Patients admitted with HF and with evidence of significant fluid overload should be treated with intravenous loop diuretics. Therapy should begin in the emergency department or outpatient clinic without delay, as early intervention may be associated with better outcomes for patients hospitalized with decompensated HF (32,567,568). (*Level of Evidence: B*) If patients are already receiving loop diuretic therapy, the initial intravenous dose should equal or exceed their chronic oral daily dose. Urine output and signs and symptoms of congestion should be serially assessed, and diuretic dose should be titrated accordingly to relieve symptoms and to reduce extracellular fluid volume excess. (*Level of Evidence: C*)
8. Effect of HF treatment should be monitored with careful measurement of fluid intake and output; vital signs; body weight, determined at the same time each day; clinical signs (supine and standing) and symptoms of systemic perfusion and congestion. Daily serum electrolytes, urea nitrogen, and creatinine concentrations should be measured during the use of IV diuretics or active titration of HF medications. (*Level of Evidence: C*)
9. When diuresis is inadequate to relieve congestion, as evidenced by clinical evaluation, the diuretic regimen should be intensified using either:
   a. higher doses of loop diuretics;
   b. addition of a second diuretic (such as metolazone, spironolactone, or intravenous chlorothiazide); or
   c. continuous infusion of a loop diuretic. (*Level of Evidence: C*)
10. In patients with clinical evidence of hypotension associated with hypoperfusion and obvious evidence of elevated cardiac filling pressures (e.g., elevated jugular venous pressure; elevated pulmonary artery wedge pressure), intravenous inotropic or vasopressor drugs should be administered to maintain systemic perfusion and preserve end-organ performance while more definitive therapy is considered. (*Level of Evidence: C*)
11. Invasive hemodynamic monitoring should be performed to guide therapy in patients who are in respiratory distress or with clinical evidence of impaired perfusion in whom the adequacy or excess of intracardiac filling pressures cannot be determined from clinical assessment. (*Level of Evidence: C*)
12. Medications should be reconciled in every patient and adjusted as appropriate on admission to and discharge from the hospital. (*Level of Evidence: C*)
13. In patients with reduced ejection fraction experiencing a symptomatic exacerbation of HF requiring hospitalization during chronic maintenance treatment with oral therapies known to improve outcomes, particularly ACEIs or ARBs and beta-blocker therapy, it is recommended that these therapies be continued in most patients in the absence of hemodynamic instability or contraindications. (*Level of Evidence: C*)
14. In patients hospitalized with HF with reduced ejection fraction not treated with oral therapies known to improve outcomes, particularly ACEIs or ARBs and beta-blocker therapy, initiation of these therapies is recommended in stable patients prior to hospital discharge (569,570). (*Level of Evidence: B*)
15. Initiation of beta-blocker therapy is recommended after optimization of volume status and successful discontinuation of intravenous diuretics, vasodilators, and inotropic agents. Beta-blocker therapy should be initiated at a low dose and only in stable patients. Particular caution should be used when initiating beta

blockers in patients who have required inotropes during their hospital course (569,570). (*Level of Evidence: B*)

16. In all patients hospitalized with HF, both with preserved (see Section 4.3.2, Patients With Heart Failure and Normal Left Ventricular Ejection Fraction) and low EF, transition should be made from intravenous to oral diuretic therapy with careful attention to oral diuretic dosing and monitoring of electrolytes. With all medication changes, the patient should be monitored for supine and upright hypotension, and worsening renal function and HF signs/symptoms. (*Level of Evidence: C*)
17. Comprehensive written discharge instructions for all patients with a hospitalization for HF and their caregivers is strongly recommended, with special emphasis on the following 6 aspects of care: diet; discharge medications, with a special focus on adherence, persistence, and uptitration to recommended doses of ACEI/ARB and beta-blocker medication; activity level; follow-up appointments; daily weight monitoring; and what to do if HF symptoms worsen. (*Level of Evidence: C*)
18. Postdischarge systems of care, if available, should be used to facilitate the transition to effective outpatient care for patients hospitalized with HF (215,571–577). (*Level of Evidence: B*)

**CLASS IIa**

1. When patients present with acute HF and known or suspected acute myocardial ischemia due to occlusive coronary disease, especially when there are signs and symptoms of inadequate systemic perfusion, urgent cardiac catheterization and revascularization is reasonable where it is likely to prolong meaningful survival. (*Level of Evidence: C*)
2. In patients with evidence of severely symptomatic fluid overload in the absence of systemic hypotension, vasodilators such as intravenous nitroglycerin, nitroprusside or nesiritide can be beneficial when added to diuretics and/or in those who do not respond to diuretics alone. (*Level of Evidence: C*)
3. Invasive hemodynamic monitoring can be useful for carefully selected patients with acute HF who have persistent symptoms despite empiric adjustment of standard therapies, and
   a. whose fluid status, perfusion, or systemic or pulmonary vascular resistances are uncertain;
   b. whose systolic pressure remains low, or is associated with symptoms, despite initial therapy;
   c. whose renal function is worsening with therapy;
   d. who require parenteral vasoactive agents; or
   e. who may need consideration for advanced device therapy or transplantation. (*Level of Evidence: C*)
4. Ultrafiltration is reasonable for patients with refractory congestion not responding to medical therapy (578). (*Level of Evidence: B*)

**CLASS IIb**

1. Intravenous inotropic drugs such as dopamine, dobutamine or milrinone might be reasonable for those patients presenting with documented severe systolic dysfunction, low blood pressure and evidence of low cardiac output, with or without congestion, to maintain systemic perfusion and preserve end-organ performance. (*Level of Evidence: C*)

**CLASS III**

1. Use of parenteral inotropes in normotensive patients with acute decompensated HF without evidence of decreased organ perfusion is not recommended (579). (*Level of Evidence: B*)
2. Routine use of invasive hemodynamic monitoring in normotensive patients with acute decompensated HF and congestion with symptomatic response to diuretics and vasodilators is not recommended (580). (*Level of Evidence: B*)

A patient may develop acute or progressive symptoms of HF and require hospitalization. In general, there are 3 clinical profiles that describe the hospitalized patient with HF: 1) the patient with volume overload, manifested by pulmonary and/or systemic congestion, frequently precipitated by an acute increase in chronic hypertension; 2) the patient with profound depression of cardiac output manifested by hypotension, renal insufficiency, and/or a shock syndrome, and 3) the patient with signs and symptoms of both fluid overload and shock. Irrespective of the presenting clinical picture, there have been a confusing variety of terms in the literature used to describe these patients, including acute HF syndrome, acute decompensated HF, or cardiogenic shock. However different these 3 groups of patients may be in outcome, they can all be characterized as having a change in HF signs and symptoms resulting in a need for urgent therapy. Patients with HF and preserved LVEF (see Section 4.3.2, Patients With Heart Failure and Normal Left Ventricular Ejection Fraction) are just as likely to be admitted to hospital as those with HF and low LVEF (581). Admission with HF is often triggered by a concomitant cardiovascular event such as a symptomatic tachyarrhythmia, unstable coronary syndrome, or a cerebrovascular event; often the admission is related to medical or dietary noncompliance. The threshold for admission may also be lowered when HF exacerbation is accompanied with a noncardiac condition such as pneumonia or newly diagnosed anemia. Indeed, it is important to note that concurrent conditions and comorbidities such as coronary artery disease, hypertension, valvular heart disease, arrhythmias, renal dysfunction, diabetes, thromboembolism, and anemia are often present, more so than has usually been described in clinical trials, and may precipitate or contribute to the pathophysiology of the syndrome. Unfortunately, the precipitating event leading to hospitalization is not always readily apparent.

### Common Factors That Precipitate Hospitalization for Heart Failure

- Noncompliance with medical regimen, sodium and/or fluid restriction
- Acute myocardial ischemia
- Uncorrected high blood pressure
- Atrial fibrillation and other arrhythmias
- Recent addition of negative inotropic drugs (e.g., verapamil, nifedipine, diltiazem, beta blockers)
- Pulmonary embolus
- Nonsteroidal anti-inflammatory drugs
- Excessive alcohol or illicit drug use
- Endocrine abnormalities (e.g., diabetes mellitus, hyperthyroidism, hypothyroidism)
- Concurrent infections (e.g., pneumonia, viral illnesses)

HF hospitalizations account for a substantial portion of the overall costs of caring for patients with HF and may be associated with a staggering degree of morbidity and mortality, particularly in the elderly population. It is evident that the prognosis after an index hospitalization for HF is ominous, with a 50% rate of readmission at 6 months and a 25% to 35% incidence of death at 12 months (582–586). Indeed, many HF trials now incorporate the need for hospitalization as an important endpoint with which to evaluate a new therapy; government agencies and insurance companies are increasingly interested in understanding the frequency of repeat HF hospitalizations. Thus, it is important to outline what should occur in the hospital for the HF patient requiring therapy. The scope of these recommendations are based on evidence from the few available randomized trials evaluating management strategies in the acute decompensated HF patient (461,578–580,587), analyses of large registries, and consensus opinion. Additional and more comprehensive information on this subject may be found in the guidelines from the Heart Failure Society of America and the European Society of Cardiology (588,589,589a).

### 4.5.1. Diagnostic Strategies

The diagnosis of HF in the hospitalized patient should be based primarily on signs and symptoms, as discussed in Section 3.1., Initial Evaluation of Patients. Clinicians need to determine as accurately and as quickly as possible 1) the volume status of the patient, 2) the adequacy of circulatory support or perfusion, and 3) the role or presence of precipitating factors and/or comorbidities. In the patient with previously established HF, efforts should likewise be directed toward understanding what has caused the apparent acute worsening of clinical symptoms. Many of the steps in this investigation are identical to those used in the initial evaluation of HF (see Sections 3.1.3, Evaluation of the Cause of Heart Failure and 3.2, Ongoing Evaluation of Patients). When the diagnosis of HF is uncertain, determination of plasma BNP or NT-proBNP concentration should be considered in patients being evaluated for dyspnea who have signs and symptoms compatible with HF. The natriuretic peptide concentration should not be interpreted in isolation but in the context of all available clinical data bearing on the diagnosis of HF.

An important cause of worsening HF, and for new-onset HF, is an acute MI. Because many patients admitted with acute HF have coronary artery disease, troponins are typically evaluated at admission for acute exacerbation. Actual criteria for an acute coronary event that may indicate the need for further intervention may be present in up to 20% of patients (590,591). However, many other patients may have low levels of detectable troponins not meeting criteria for an acute ischemic event but typical of chronic HF with an acute exacerbation (592). Registry data have suggested that the use of coronary angiography is low for patients hospitalized with decompensated HF and opportunities to diagnose important coronary artery disease may be missed. Symptoms of HF or cardiogenic shock associated with an ischemic event are covered in other guidelines (10,593) and are beyond the scope of this update. For the patient with newly discovered HF, clinicians should be aware of the important role of coronary artery disease in causing HF and should be certain that coronary structure and function are well delineated (see Section 3.1.2, Identification of a Structural and Functional Abnormality) while simultaneously beginning treatment. Coronary visualization may be an important part of the evaluation of patients hospitalized with HF.

Often, patients with chronic HF are admitted with acute decompensation from a number of possible precipitating causes. Clinicians should carefully review the patient's maintenance HF medications and decide whether adjustments should be made as a result of the hospitalization. The large majority of patients with HF admitted to the hospital, especially those with concomitant hypertension, should have their oral therapy continued, or even uptitrated, during hospitalization. It is important to note that it has been shown that continuation of beta blockers for most patients is well tolerated and results in better outcomes (569,570). Withholding of or reduction in beta-blocker therapy should be considered only in patients hospitalized after recent initiation or increase in beta-blocker therapy or with marked volume overload. Patients admitted with worsening azotemia should be considered for a reduction in or temporary discontinuation of their ACEIs, ARBs, and/or aldosterone antagonists until renal function improves. Patients with marked volume overload will require intravenous diuretic therapy with uptitration of diuretic dose and/or addition of synergistic diuretic agents. It should be noted that uptitration of ACEIs or beta blockers during decompensation may reduce the efficacy of the acute interventions to relieve congestion. Although it is important to ensure that evidence-based medications are instituted prior to the patient leaving the hospital, it is equally as critical to reassess medications on admission and to adjust their administration in light of the worsening HF.

### 4.5.2. Treatment in the Hospital

#### 4.5.2.1. DIURETICS: THE PATIENT WITH VOLUME OVERLOAD

Patients admitted with evidence of significant fluid overload should initially be treated with loop diuretics, usually given intravenously. Therapy for this compelling presentation of HF should begin in the emergency department and should be initiated without delay. Early intervention has been associated with better outcomes for patients hospitalized with decompensated HF (594,595). After admission to the hospital, patients should be carefully monitored in accordance with the severity of their symptoms and the results of initial findings on the physical examination and laboratory assessment. Careful and frequent serial evaluation of the patient is important primarily to assess volume status (see Section 3.2.2, Assessment of Volume Status) and adequacy of circulatory support. Laboratory parameters are likewise

necessary to judge efficacy of treatment (see Sections 3.1.3.2, Laboratory Testing, and 3.2.3, Laboratory Assessment). Monitoring of daily weight, supine and standing vital signs, fluid input, and output is a necessary part of daily management; assessment of daily electrolytes and renal function should be done while intravenous diuretics or active HF medication titration is being undertaken.

Intravenous loop diuretics have the potential to reduce glomerular filtration rate (GFR), further worsen neurohumoral activation, and produce electrolyte disturbances. Thus, although the use of diuretics may result in the effective relief of symptoms, their impact on mortality has not been well studied. Diuretics should be administered at doses sufficient to produce a rate of diuresis that will optimize volume status and relieve signs and symptoms of congestion without inducing an excessively rapid reduction in intravascular volume, which could result in hypotension, renal dysfunction, or both (see Sections 4.3.1.2.1, Diuretics, and 4.4.1, Management of Fluid Status). Because loop diuretics have a relatively short half-life, sodium reabsorption in the tubules will occur once the tubular concentration of the diuretics declines. Therefore, strictly limiting sodium intake and dosing the diuretic multiple times per day will enhance effectiveness of the diuresis (275–279,596–598). Some patients may present with congestion and moderate to severe renal dysfunction. The response to diuretics may be significantly blunted, requiring higher initial doses. In many cases, reduction of fluid overload may improve not only congestion but also renal dysfunction, particularly if significant venous congestion is reduced (599).

Clinical experience suggests it is difficult to determine whether congestion has been adequately treated in many patients, and registry data have confirmed that patients are frequently discharged after a net weight loss of only a few pounds. Although patients may rapidly improve symptomatically, they may remain hemodynamically compromised. Unfortunately, the routine use of serial natriuretic peptide measurement (BNP or NT-proBNP) or even a Swan-Ganz catheter to monitor hemodynamics has not been shown to be helpful in improving the outcomes of the hospitalized patient with HF. Nevertheless, careful evaluation of all physical findings, laboratory parameters, weight change, and net fluid change should be considered before discharge planning is commenced.

When a patient with congestion fails to respond to initial doses of intravenous diuretics, several options may be considered. Efforts should be taken to make certain that, indeed, congestion persists and that another hemodynamic profile or perhaps another disease process is not evident. This is particularly important for the patient with progressive renal insufficiency. If there is substantial doubt about the fluid status of the patient, HF experts suggest that it is an appropriate time for a formal hemodynamic assessment of ventricular filling pressures and cardiac output, typically done with a right heart catheterization. If volume overload is confirmed, the dose of the loop diuretic should be initially increased to ensure that adequate drug levels reach the kidney. If this is inadequate, a second type of diuretic, typically a thiazide (metolazone or intravenous chlorothiazide) or spironolactone, can be added to improve diuretic responsiveness. As a third strategy, continuous infusion of the loop diuretic may be considered. By continuous delivery of the diuretic to the nephron, rebound resorption occurring during the time blood levels of diuretic are low is avoided and ototoxicity risk may actually be reduced (see Sections 4.3.1.2.1, Diuretics, and 4.4.1, Management of Fluid Status) (279,280,282–286,598,600,601). If all diuretic strategies are unsuccessful, ultrafiltration or another renal replacement strategy may be reasonable. Ultrafiltration moves water and small- to medium-weight solutes across a semipermeable membrane to reduce volume overload. Because the electrolyte concentration is similar to plasma, relatively more sodium can be removed than by diuretics (529,578,602–604). Consultation with a kidney specialist may be appropriate before opting for any mechanical strategy to affect diuresis.

#### 4.5.2.2. VASODILATORS

There are a number of clinical scenarios whereby the addition of vasodilators to the HF regimen of the hospitalized patient might be appropriate. For patients with adequate blood pressure and ongoing congestion not sufficiently responsive to diuretics and standard oral therapy (e.g., maintenance of prior HF medications, if applicable), intravenous vasodilators such as nitroprusside, nitroglycerin, or nesiritide may be added to the treatment regimen. Regardless of the agent used, the clinician should make certain that intravascular volume is, in fact, expanded and that the patient's blood pressure can tolerate the addition of the vasodilating drug.

Intravenous nitroglycerin, primarily through venodilation effects, lowers preload and may help to more rapidly reduce pulmonary congestion. Patients with HF and hypertension, coronary ischemia, or significant mitral regurgitation are often cited as ideal candidates for the use of intravenous nitroglycerin. However, tachyphylaxis to nitroglycerin may develop rather quickly and up to 20% of those with HF may develop resistance to even high doses (605–607). Sodium nitroprusside is a balanced preload-reducing venodilator and afterload-reducing arteriodilator that also dilates the pulmonary vasculature. Data demonstrating efficacy are limited, and invasive hemodynamic blood pressure monitoring is typically required. Nitroprusside has the potential for producing marked hypotension and is usually used in the intensive care setting as well; longer infusions of the drug have been associated with thiocyanate toxicity, particularly in the setting of renal insufficiency. Nitroprusside is potentially of value in severely congested patients with hypertension or severe mitral valve regurgitation complicating LV dysfunction. Nesiritide (human BNP) reduces LV filling pressure but has variable effects on cardiac output, urinary output, and sodium excretion. The severity of dyspnea is

reduced more rapidly compared to diuretics alone. Because nesiritide has a longer effective half-life than nitroglycerin or nitroprusside, side effects such as hypotension may persist longer. Conservative dosing of the drug (i.e., no bolus) and use of only the recommended doses may reduce complications. Adverse renal consequences with nesiritide have been suggested; careful monitoring of renal function is mandatory (459,461–463,608–610). The effects of nesiritide on mortality remain uncertain and active clinical investigation is ongoing.

The role of intravenous vasodilators for the patient hospitalized with HF can not be generalized. The goals of HF therapy with vasodilators, in the absence of more definitive data, include a more rapid resolution of congestive symptoms; relief of anginal symptoms while awaiting coronary intervention; control of hypertension complicating HF; and, in conjunction with ongoing hemodynamic monitoring while the intravenous drug is administered, improvement of hemodynamic abnormalities prior to instituting oral HF medications.

#### 4.5.2.3. INOTROPES

Patients presenting with either predominantly low output syndrome (e.g., symptomatic hypotension) or combined congestion and low output may be considered for intravenous inotropes such as dopamine, dobutamine, and milrinone. These agents may help relieve symptoms due to poor perfusion and preserve end-organ function in patients with severe systolic dysfunction and dilated cardiomyopathy. Inotropic agents are of greatest value in patients with relative hypotension and intolerance or no response to vasodilators and diuretics. Clinicians should be cautioned again that the use of these drugs portends a very poor prognosis for their patients; a thorough hemodynamic assessment must be undertaken to ensure that the low output syndrome is responsible for the presenting clinical signs and symptoms. Likewise, clinicians should not use a specific blood pressure value that might or might not mean hypotension, to dictate the use of inotropic agents. Rather, a depressed blood pressure associated with signs of poor cardiac output or hypoperfusion (e.g., cold clammy skin, cool extremities, decreased urine output, altered mentation) should prompt a consideration for more aggressive intravenous therapy. Dobutamine requires the beta-receptor for its inotropic effects, while milrinone does not. This may be a significant consideration for patients already maintained on beta-blocking drugs. Furthermore, milrinone has vasodilating properties for both the systemic circulation and the pulmonary circulation. Despite these considerations, there is no evidence of benefit for routine use of inotropic support in patients presenting with acute HF due to congestion only (579,611–613). Indeed, data from several studies suggest an increase in adverse outcomes when inotropes are used. Thus, inotropes should be confined to carefully selected patients with low blood pressure and reduced cardiac output who can have blood pressure and heart rhythm monitored closely (see Section 4.4.3, Intravenous Peripheral Vasodilators and Positive Inotropic Agents).

Routine invasive hemodynamic monitoring is not indicated for most patients hospitalized with symptoms of worsening HF. Recent evaluations of the use of right heart catheterization to improve outcomes have been essentially neutral with regard to overall benefit (580,614). However, hemodynamic monitoring should be strongly considered in patients whose volume and filling pressures are uncertain or who are refractory to initial therapy, particularly in those whose filling pressures and cardiac output are unclear. Patients with clinically significant hypotension (systolic blood pressure typically less than 90 mm Hg or symptomatic low systolic blood pressure) and/or worsening renal function during initial therapy might also benefit. Patients being considered for cardiac transplantation or placement of a mechanical circulatory support device are also candidates for complete right heart catheterization, a necessary part of the initial evaluation (see Section 4.4.4, Mechanical and Surgical Strategies). Invasive hemodynamic monitoring should be performed in patients with 1) presumed cardiogenic shock requiring escalating pressor therapy and consideration of mechanical support; 2) severe clinical decompensation in which therapy is limited by uncertainty regarding relative contributions of elevated filling pressures, hypoperfusion, and vascular tone; 3) apparent dependence on intravenous inotropic infusions after initial clinical improvement; or 4) persistent severe symptoms despite adjustment of recommended therapies. This reinforces the concept that right heart catheterization is best reserved for those situations where a specific clinical or therapeutic question needs to be addressed.

#### 4.5.2.4. OTHER CONSIDERATIONS

Other treatment or diagnostic strategies may be necessary for individual patients after stabilization, particularly related to the underlying cause of the acute event. Considerations are similar to those previously discussed in Section 3.1.3, Evaluation of the Cause of Heart Failure. The patient hospitalized with HF is at increased risk for thromboembolic complications and deep venous thrombosis and should receive prophylactic anticoagulation with either intravenous unfractionated heparin or subcutaneous preparations of unfractionated or low-molecular-weight heparin, unless contraindicated (615).

As the hospitalized patient becomes more clinically stable and volume status normalizes, oral HF therapy should be initiated or reintroduced (see Sections 4.3.1, Patients With Reduced Left Ventricular Ejection Fraction, and 4.3.2, Patients With Heart Failure and Normal Left Ventricular Ejection Fraction). Particular caution should be used when initiating beta blockers in patients who have required inotropes during their hospital course or when initiating ACEIs in those patients who have experienced marked azotemia. During additional hospital days, the patient should be fully transitioned off all intravenous therapy, and oral therapy should be adjusted and maximized. The clinical

team should provide further education about HF to both the patient and family. The treating clinicians should also reassess overall prognosis once current functional status and precipitating causes of the hospitalization have been determined. The appropriateness of discussion about advanced therapy or end-of-life preferences should also be considered (see Sections 3.2.4, Assessment of Prognosis, and 7, End-of-Life Considerations). On discharge, the patient, the family, and the patient's primary physician should be aware and supportive of the follow-up plans.

### 4.5.3. The Hospital Discharge

To ensure safe, high-quality, and efficient care for patients following hospitalization for HF, the consistent use of clinical practice guidelines developed by the ACCF, the AHA, and the Heart Failure Society of America should be promoted during and after the hospital stay. One critical performance measure for care coordination and transition is that of written discharge instructions or educational material given to patient and/or caregiver at discharge to home or during the hospital stay addressing all of the following: activity level, diet, discharge medications, follow-up appointment, weight monitoring, and what to do if symptoms worsen (616). Education of HF patients and their families is critical and often complex. Failure of these patients to understand how best to comply with physician's and other healthcare providers' instructions is often a cause of HF exacerbation leading to subsequent hospital readmission.

Large registries of hospitalized HF patients suggest that many patients are discharged before optimal volume status is achieved, or sent home without the benefit of life-saving therapies such as ACE/ARB and beta-blocker medications. Among hospitals providing care for patients with HF, there is significant individual variability in conformity to quality-of-care indicators and clinical outcomes and a substantial gap in overall performance (617). Patients are discharged without adequate control of their blood pressure or the ventricular response to atrial fibrillation. Often, the treating clinician fails to appreciate the severity of the HF process or delays diagnostic testing until the patient is seen as an outpatient. These problems, and others, may account for the high rate of HF rehospitalizations seen in the United States.

It is, therefore, incumbent on healthcare professionals to be certain that patients and their families have an understanding of the causes of HF, prognosis, therapy, dietary restrictions, activity, importance of compliance, and signs and symptoms of recurrent HF. Thorough discharge planning that includes a special emphasis on ensuring compliance with an evidence-based medication regimen (571) is associated with improved patient outcomes (572,618,619).

Several studies have examined the effect of providing more intensive delivery of discharge instructions coupled tightly with subsequent well-coordinated follow-up care for patients hospitalized with HF, many with positive results (215,573–575). Comprehensive discharge planning plus postdischarge support for older patients with HF can significantly reduce readmission rates and may improve health outcomes such as survival and quality of life without increasing costs. A meta-analysis (576) of 18 studies representing data from 8 countries randomized 3304 older inpatients with HF to comprehensive discharge planning plus postdischarge support or usual care. During a mean observation period of 8 months, fewer intervention patients were readmitted compared with controls. Analysis of studies reporting secondary outcomes found a trend toward lower all-cause mortality, length of stay, hospital costs, and improvement in quality-of-life scores for patients assigned to an intervention compared with usual care. One other important study (577) focusing on hospital discharge for patients with HF demonstrated that the addition of a 1-hour, nurse educator–delivered teaching session at the time of hospital discharge using standardized instructions resulted in improved clinical outcomes, increased self-care measure adherence, and reduced cost of care. Patients receiving the education intervention had a lower risk of rehospitalization or death and lower costs of care.

The importance of patient safety for all patients hospitalized with HF cannot be overemphasized. Meaningful evidence has facilitated a much better understanding of the systems changes necessary to achieve safer care. This includes the adoption by all U.S. hospitals of a standardized set of 30 "Safe Practices" endorsed by the National Quality Forum (620), which overlap in many ways with the National Patient Safety Goals espoused by The Joint Commission (621). Improved communication between physicians and nurses, medication reconciliation, transitions between care settings, and consistent documentation are examples of patient safety standards that should be ensured for patients discharged from the hospital with HF. Care information, especially changes in orders and new diagnostic information, must be transmitted in a timely and clearly understandable form to all of the patient's current healthcare providers who need that information to provide follow-up care.

Hospitalization is in and of itself an independent risk factor for shortened survival in patients with chronic HF. Hence, appropriate levels of symptomatic relief, support, and palliative care for patients with chronic HF should be addressed as an ongoing key component of their plan of care, especially when hospitalized with acute decompensation (622). Fortunately, most US hospitals today have direct access to palliative care services (623). Good evidence exists for the critical importance of delivering comprehensive supportive care to these patients, including the assessment and treatment of dyspnea and physiological issues including anxiety and depression (624,625,625a,625b).

## 5. Treatment of Special Populations (UPDATED)

*The recommendations for hydralazine/isosorbide dinitrate in a specific population have been clarified in this section and in a*

*previous section (223,236), based on a recent multicenter trial (Table 6).*

### Recommendations

**CLASS I**

1. **The combination of a fixed dose of isosorbide dinitrate and hydralazine to a standard medical regimen for HF, including ACEIs and beta blockers, is recommended in order to improve outcomes for patients self-described as African Americans, with NYHA functional class III or IV HF. Others may benefit similarly, but this has not yet been tested (223,236). (*Level of Evidence: A*)**
2. **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 (626,627). (*Level of Evidence: B*)**
3. **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*)**

## 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 (48). 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 (628), and another study reported that women are given fewer cardiovascular medications after an MI than men (564,629,630). 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 (564). Some analyses have suggested that women with HF, particularly with asymptomatic reduced LVEF, may not show survival benefits from ACE inhibition (631,632). Women may also have a different safety profile than men, as evidenced by their higher risk of ACEI-induced cough (633). 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 (379). 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 (634). 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 (635).

## 5.2. Ethnic Considerations

Race is an imprecise concept that has largely become a social and political construct, with more limited biological significance (636). 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 (637–639). 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 (637–639).

The literature is mixed on whether blacks with HF more frequently receive suboptimal inpatient care for their HF (640,641). 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 (642–644).

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 (222). 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 (645). However, rates of death in that trial were similar between black and nonblack patients with HF (645). 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 (646). 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 (647). There may be race-based differences in the outcome of cardiac transplantation as well (648). 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 (649–652). Data from these early investigations are not yet definitive; racial groupings are necessarily heterogenous, 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 (223). 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 (223).

### 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 (653), and HF is the most common reason for hospitalization in elderly patients (654–657). 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 (658–662). 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) (187).

Heart failure in elderly patients is inadequately recognized and treated (662). 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 (663–665) compared with younger patients and may experience a higher risk of adverse effects attributable to treatment (630,666–670). 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 (258,671). Managed care organizations continue to struggle to find improved ways to implement these pathways (672,673).

## 6. Patients With Heart Failure Who Have Concomitant Disorders (UPDATED)

### 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 (674). Both disorders can contribute to the development of systolic or diastolic dysfunction (675,676), either directly or by contributing (together with hyperlipidemia) to the development of coronary artery disease (677,678). Long-term treatment of both hypertension and hyperlipidemia decreases the risk of developing HF (72,73,679,680). 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 (679). 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 (72,73,680). The benefits of lowering blood pressure may be particularly marked in patients with diabetes mellitus (80,82,681).

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 (682,683), and the resulting hyperinsulinemia may promote both cardiac and vascular hypertrophy (684–686) 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 (92).

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 (687,688).

*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) (679) 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) (72,73,679,680). 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 (689,690). 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 (157,162,691). 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 (692). 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 (158,162,164,693,694). 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 (695).

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 (696–698). These drugs have not improved symptoms of HF or enhanced exercise tolerance (695–699), 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 (135,700–708). 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 (242).

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 (709,710), 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 (711) (see the ACC/AHA/ACPASIM Guidelines for the Management of Patients With Chronic Stable Angina [712] or the ACC/AHA 2004 Guideline Update for Coronary Artery Bypass Graft Surgery [16]).

*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 (83,123,124,129); drugs to address dyslipidemia, such as statins; antiplatelet drugs such as aspirin and clopidogrel (310,312); and coronary revascularization (709). 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 (126–128,713,714), 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 (709), and concerns have been raised that it may attenuate the hemodynamic and survival benefits of ACEIs (303,306,307). 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 (305) and may have superior effects in preventing clinical events (312), 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 (715). 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 (716–718) and may also reduce the risk of a fatal coronary occlusion in patients with established multivessel disease (717). Despite these theoretical possibilities, however, coronary revascularization has not been shown to improve cardiac function or symptoms or to prevent reinfarction or death in patients with HF and no angina (15,719).

### 6.1.3. Supraventricular Arrhythmias (UPDATED)

There have been additional trials investigating the appropriate management of atrial fibrillation in patients with HF. The text has been modified to reflect the lessons learned from these trials (see Section 4.3.1, Patients With Reduced Left Ventricular Ejection Fraction). There is also an ACC/AHA/ESC guideline on the management of atrial fibrillation (720).

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 (721–723).

Supraventricular tachyarrhythmias may exert adverse effects via 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) (724,725) and cardiac relaxation (726,727); 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 (728). 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 (136,137). Hence, the control of ventricular rate and the prevention of thromboembolic events are essential elements of treatment of HF in patients with an underlying supraventricular arrhythmia (729,730). 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 previously 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 (365,731). Hence, digitalis does not block the excessive exercise-induced tachycardia that may limit the functional capacity of patients with HF (363–365,731). Beta blockers are more effective than digoxin during exercise (363,365) and are preferred because of their favorable effects on the natural history of HF (158,162,164). 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 worsening HF, especially in patients with HF and low EF, in whom these drugs should be avoided (703,705). If beta blockers are ineffective or contraindicated in patients with atrial fibrillation and HF, amiodarone may be a useful alternative (732). Atrioventricular nodal ablation may be needed if tachycardia persists despite pharmacological therapy (387). Catheter ablation for pulmonary vein isolation has been most effective in patients without structural heart disease; the benefit for patients with established HF is not known (733–735). Regardless of the intervention used, every effort should be made to reduce the ventricular response to less than 80 to 90 bpm at rest and less than 110 to 130 bpm 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, unless a contraindication exists (730).

Should patients with HF and atrial fibrillation be converted to and maintained in sinus rhythm? The efficacy and safety of restoring and maintaining sinus rhythm in patients with atrial fibrillation were evaluated in a total of 5032 patients in 4 separate trials (736). Both strategies for the management of atrial fibrillation, either to restore and maintain sinus rhythm by electrical or pharmacologic conversion, or to control ventricular rate in atrial fibrillation, have been shown to have equivalent outcomes. These results were confirmed in 2007 with the conclusion of a large trial of patients with both atrial fibrillation and HF (226,227,730). Most patients revert to atrial fibrillation within a short time unless they are treated with a Class I or III antiarrhythmic drug (721). 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 (193,247), which can increase the risk of death (191,192,388). Class III antiarrhythmic agents (e.g., sotalol, 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) (737,738) and proarrhythmia (dofetilide) (248). Most patients who had thromboembolic events, regardless of the strategy used, were in atrial fibrillation at the time of the event and either were not undergoing anticoagulation therapy or were undergoing therapy at subtherapeutic levels. Thus, it is reasonable to treat HF patients with atrial fibrillation with a strategy of either scrupulous rate control or an attempt at rhythm control.

### 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 (739,740) and perhaps due to increased activity of procoagulant factors (741). 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 (742–746). 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 (742,744,745). 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 (747–749). 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 (739). Others would advocate the use of warfarin in patients who are known to harbor a cardiac thrombus (740), even though many thrombi detected by echocardiography do not embolize and many embolic events are probably related to thrombi that are not visualized (293,750). 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 (730). Anticoagulation should also be considered in patients with underlying disorders that may be associated with an increased thromboembolic risk (e.g., amyloidosis or LV noncompaction) and in patients with familial dilated cardiomyopathy and a history of thromboembolism in first-degree relatives.

## 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 (275,751) and are at increased risk of adverse effects during treatment with digitalis (370). Renal function may worsen during treatment with diuretics or ACEIs (274,527), 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 (41,752). The symptoms of HF in patients with end-stage renal disease may be exacerbated by an increase in loading conditions produced both by anemia (753) 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 (275,370,751). 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 (548,754).

### 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 (755).

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 reinstitution 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 (756). 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 (757), high-dose cyclophosphamide (758–762), and trastuzumab (763). Trastuzumab is a monoclonal antibody recently approved for therapy of metastatic breast cancer (764) 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 ar-

teries, particularly when used in conjunction with cardiotoxic chemotherapy (765).

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 (766), 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 (767,768). 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 reevaluation of thyroid status.

### 6.2.5. Patients With Hepatitis C and Human Immunodeficiency Virus

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 (514,515). 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 (516,769). A small study showed that hepatitis C virus myocarditis might respond favorably to immunosuppressive therapy with prednisone and azathioprine (770,771). Preliminary data also suggest that this type of myocarditis might respond well to interferon therapy (515), 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 (772). 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 (773). Drug therapy for HIV with zidovudine has also been implicated as a cause of cardiomyopathy, possibly through its effect on cardiac myocyte mitochondrial function (774). 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 (775).

### 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 (776,777). 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 (778–780). 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 reevaluation 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**

1. **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 (781). These frequencies are higher than those seen in other chronic diseases (782), 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 (783) 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 (784). The majority of patients with HF who had not discussed resuscitation during hospitalization indicated that they had not desired such an interaction (781). 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 (785).

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 (786). 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 (787). 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 (622,788). 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 (789). 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 (790) 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 endstage 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 (788).

# 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**

1. **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 (262,791), 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 (630,792,793). 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 (549,794,795). Many HF admissions may be prevented with good outpatient care (796). 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 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 (797). Indeed, an extensive literature has documented how difficult it is to produce appropriate changes in physician behavior (798–800). 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 (801). 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 (261,802). 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 (803). 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 (258). 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 (804).

The ACCF and AHA are collaborating with a variety of organizations to develop and implement performance measures. ACCF/AHA practice guidelines are useful starting points for performance measures, but several considerations apply: 1) ACCF/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 measures 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 (805–807). Some studies have noted better patient outcomes in patients cared for by cardiologists than in those cared for by generalist physicians (808,809), whereas another study reported that cardiologists deliver more costly care that is accompanied by a trend toward improved survival (810). 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.

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## REFERENCES

1. ACC/AHA Task Force on Practice Guidelines. Manual for ACC/AHA Guideline Writing Committees: Methodologies and Policies from the ACC/AHA Task Force on Practice Guidelines. 2006. Available at: http://www.acc.org/qualityandscience/clinical/manual/pdfs/methodology.pdf and http://circ.ahajournals.org/manual/. Accessed January 30, 2008.
2. Hunt SA, Abraham WT, Chin MH, et al. 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). J Am Coll Cardiol. 2005;46:e1–82.
3. 2009 Focused Update: ACCF/AHA guidelines for the diagnosis and management of heart failure in adults: a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines. J Am Coll Cardiol. 2009;53:1343–82.
4. American Heart Association. Heart Disease and Stroke Statistics–2005 Update. Dallas, TX: American Heart Association; 2005.
5. O'Connell JB, Bristow MR. Economic impact of heart failure in the United States: time for a different approach. J Heart Lung Transplant. 1994;13 Suppl:S107–12.
6. Koelling TM, Chen RS, Lubwama RN, et al. The expanding national burden of heart failure in the United States: the influence of heart failure in women. Am Heart J. 2004;147:74–8.
7. Kannel WB, Belanger AJ. Epidemiology of heart failure. Am Heart J. 1991;121:951–7.
8. Masoudi FA, Havranek EP, Krumholz HM. The burden of chronic congestive heart failure in older persons: magnitude and implications for policy and research. Heart Fail Rev. 2002;7:9–16.
9. Massie BM, Shah NB. Evolving trends in the epidemiologic factors of heart failure: rationale for preventive strategies and comprehensive disease management. Am Heart J. 1997;133:703–12.
10. Hunt SA, Baker DW, Chin MH, et al. ACC/AHA guidelines for the evaluation and management of chronic heart failure in the adult: executive summary. A report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (Committee to Revise the 1995 Guidelines for the Evaluation and Management of Heart Failure). J Am Coll Cardiol. 2001;38:2101–13.
11. Antman EM, Anbe DT, Armstrong PW, et al. ACC/AHA guidelines for the management of patients with ST-elevation myocardial infarction; A report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (Committee to Revise the 1999 Guidelines for the Management of patients with acute myocardial infarction). J Am Coll Cardiol. 2004;44:e1–211.
12. Braunwald E, Antman EM, Beasley JW, et al. ACC/AHA 2002 guideline update for the management of patients with unstable angina and non-ST-segment elevation myocardial infarction—summary article: a report of the American College of Cardiology/American Heart Association task force on practice guidelines (Committee on the Management of Patients With Unstable Angina). J Am Coll Cardiol. 2002;40:1366–74.
13. Bonow RO, Carabello BA, Chatterjee K, et al. ACC/AHA 2006 guidelines for the management of patients with valvular heart disease: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (Writing Committee to Revise the 1998 Guidelines for the Management of Patients With Valvular Heart Disease). J Am Coll Cardiol. 2006;48:e1–148.
14. Francis GS, Pierpont GL. Pathophysiology of congestive heart failure secondary to congestive and ischemic cardiomyopathy. In: Shaver JA, editor. Cardiomyopathies: Clinical presentation, differential diagnosis, and management. Philadelphia: F.A. Davis, 1988:57–74.
15. Alderman EL, Fisher LD, Litwin P, et al. Results of coronary artery surgery in patients with poor left ventricular function (CASS). Circulation. 1983;68:785–95.
16. Eagle KA, Guyton RA, Davidoff R, et al. ACC/AHA 2004 guideline update for coronary artery bypass graft surgery: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (Committee to Update the 1999 Guidelines for Coronary Artery Bypass Graft Surgery). Circulation. 2004;110:e340–7.
17. Fox KF, Cowie MR, Wood DA, et al. Coronary artery disease as the cause of incident heart failure in the population. Eur Heart J. 2001;22:228–36.
18. Arques S, Ambrosi P, Gelisse R, et al. Prevalence of angiographic coronary artery disease in patients hospitalized for acute diastolic heart failure without clinical and electrocardiographic evidence of myocardial ischemia on admission. Am J Cardiol. 2004;94:133–5.
19. Kurtz CE, Gerber Y, Weston SA, et al. Use of ejection fraction tests and coronary angiography in patients with heart failure. Mayo Clin Proc. 2006;81:906–13.
20. Elhendy A, Schinkel AF, van Domburg RT, et al. Incidence and predictors of heart failure during long-term follow-up after stress Tc-99m sestamibi tomography in patients with suspected coronary artery disease. J Nucl Cardiol. 2004;11:527–33.
21. Chomsky DB, Lang CC, Rayos GH, et al. Hemodynamic exercise testing. A valuable tool in the selection of cardiac transplantation candidates. Circulation. 1996;94:3176–83.
22. Gullestad L, Myers J, Ross H, et al. Serial exercise testing and prognosis in selected patients considered for cardiac transplantation. Am Heart J. 1998;135:221–9.
23. Mehra MR, Kobashigawa J, Starling R, et al. Listing criteria for heart transplantation: International Society for Heart and Lung Transplantation guidelines for the care of cardiac transplant candidates—2006. J Heart Lung Transplant. 2006;25:1024–42.
24. Cooper LT, Baughman KL, Feldman AM, et al. The role of endomyocardial biopsy in the management of cardiovascular disease: a scientific statement from the American Heart Association, the American College of Cardiology, and the European Society of Cardiology. Circulation. 2007;116:2216–33.
25. de Lemos JA, McGuire DK, Drazner MH. B-type natriuretic peptide in cardiovascular disease. Lancet. 2003;362:316–22.
26. Siebert U, Januzzi JL Jr., Beinfeld MT, et al. Cost-effectiveness of using N-terminal pro-brain natriuretic peptide to guide the diagnostic assessment and management of dyspneic patients in the emergency department. Am J Cardiol. 2006;98:800–5.
27. Gackowski A, Isnard R, Golmard JL, et al. Comparison of echocardiography and plasma B-type natriuretic peptide for monitoring the response to treatment in acute heart failure. Eur Heart J. 2004;25:1788–96.
28. Bayes-Genis A, Santalo-Bel M, Zapico-Muniz E, et al. N-terminal probrain natriuretic peptide (NT-proBNP) in the emergency diagnosis and in-hospital monitoring of patients with dyspnoea and ventricular dysfunction. Eur J Heart Fail. 2004;6:301–8.
29. Dao Q, Krishnaswamy P, Kazanegra R, et al. Utility of B-type natriuretic peptide in the diagnosis of congestive heart failure in an urgent-care setting. J Am Coll Cardiol. 2001;37:379–85.
30. Worster A, Balion CM, Hill SA, et al. Diagnostic accuracy of BNP and NT-proBNP in patients presenting to acute care settings with dyspnea: a systematic review. Clin Biochem. 2008;41:250–9.
31. O'Donoghue M, Kenney P, Oestreicher E, et al. Usefulness of aminoterminal pro-brain natriuretic peptide testing for the diagnostic and prognostic evaluation of dyspneic patients with diabetes mellitus seen in the emergency department (from the PRIDE Study). Am J Cardiol. 2007;100:1336–40.
32. Silvers SM, Howell JM, Kosowsky JM, et al. Clinical policy: Critical issues in the evaluation and management of adult patients presenting to the emergency department with acute heart failure syndromes. Ann Emerg Med. 2007;49:627–69.
33. Gibbons RJ, Balady GJ, Bricker JT, et al. ACC/AHA 2002 guideline update for exercise testing: summary article. A report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (Committee to Update the 1997 Exercise Testing Guidelines). J Am Coll Cardiol. 2002;40:1531–40.

34. The Criteria Committee of the New York Heart Association. Diseases of the heart and blood vessels: nomenclature and criteria for diagnosis. 6th edition. Boston: Little, Brown, 1964.
35. Vitarelli A, Tiukinhoy S, Di LS, et al. The role of echocardiography in the diagnosis and management of heart failure. Heart Fail Rev. 2003;8:181–9.
36. Ritchie JL, Bateman TM, Bonow RO, et al. Guidelines for clinical use of cardiac radionuclide imaging. Report of the American College of Cardiology/American Heart Association Task Force on Assessment of Diagnostic and Therapeutic Cardiovascular Procedures (Committee on Radionuclide Imaging), developed in collaboration with the American Society of Nuclear Cardiology. J Am Coll Cardiol. 1995;25:521–47.
37. Bello D, Shah DJ, Farah GM, et al. Gadolinium cardiovascular magnetic resonance predicts reversible myocardial dysfunction and remodeling in patients with heart failure undergoing beta-blocker therapy. Circulation. 2003;108:1945–53.
38. Drazner MH, Rame JE, Stevenson LW, et al. Prognostic importance of elevated jugular venous pressure and a third heart sound in patients with heart failure. N Engl J Med. 2001;345:574–81.
39. Mestroni L. Genomic medicine and atrial fibrillation. J Am Coll Cardiol. 2003;41:2193–6.
40. Troughton RW, Frampton CM, Yandle TG, et al. Treatment of heart failure guided by plasma aminoterminal brain natriuretic peptide (N-BNP) concentrations. Lancet. 2000;355:1126–30.
41. Weinfeld MS, Chertow GM, Stevenson LW. Aggravated renal dysfunction during intensive therapy for advanced chronic heart failure. Am Heart J. 1999;138:285–90.
42. Maisel A. B-type natriuretic peptide levels: a potential novel "white count" for congestive heart failure. J Card Fail. 2001;7:183–93.
43. Mueller C, Scholer A, Laule-Kilian K, et al. Use of B-type natriuretic peptide in the evaluation and management of acute dyspnea. N Engl J Med. 2004;350:647–54.
44. Wang TJ, Larson MG, Levy D, et al. Impact of obesity on plasma natriuretic peptide levels. Circulation. 2004;109:594–600.
45. Mehra MR, Uber PA, Park MH, et al. Obesity and suppressed B-type natriuretic peptide levels in heart failure. J Am Coll Cardiol. 2004;43:1590–5.
46. Wright SP, Doughty RN, Pearl A, et al. Plasma amino-terminal pro-brain natriuretic peptide and accuracy of heart-failure diagnosis in primary care: a randomized, controlled trial. J Am Coll Cardiol. 2003;42:1793–800.
47. Gheorghiade M, Bonow RO. Chronic heart failure in the United States: a manifestation of coronary artery disease. Circulation. 1998; 97:282–9.
48. Masoudi FA, Havranek EP, Smith G, et al. Gender, age, and heart failure with preserved left ventricular systolic function. J Am Coll Cardiol. 2003;41:217–23.
49. Smith GL, Masoudi FA, Vaccarino V, et al. Outcomes in heart failure patients with preserved ejection fraction: mortality, readmission, and functional decline. J Am Coll Cardiol. 2003;41:1510–8.
50. Allman KC, Shaw LJ, Hachamovitch R, et al. Myocardial viability testing and impact of revascularization on prognosis in patients with coronary artery disease and left ventricular dysfunction: a meta-analysis. J Am Coll Cardiol. 2002;39:1151–8.
51. Cheitlin MD, Armstrong WF, Aurigemma GP, et al. ACC/AHA/ASE 2003 Guideline Update for the Clinical Application of Echocardiography: summary article. A report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (ACC/AHA/ASE Committee to Update the 1997 Guidelines for the Clinical Application of Echocardiography). J Am Soc Echocardiogr. 2003;16:1091–110.
52. Klocke FJ, Baird MG, Lorell BH, et al. ACC/AHA/ASNC guidelines for the clinical use of cardiac radionuclide imaging—executive summary: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (ACC/AHA/ASNC Committee to Revise the 1995 Guidelines for the Clinical Use of Cardiac Radionuclide Imaging). J Am Coll Cardiol. 2003;42: 1318–33.
53. Lie JT. Myocarditis and endomyocardial biopsy in unexplained heart failure: a diagnosis in search of a disease. Ann Intern Med. 1988; 109:525–8.
54. Chow LC, Dittrich HC, Shabetai R. Endomyocardial biopsy in patients with unexplained congestive heart failure. Ann Intern Med. 1988;109:535–9.
55. Mason JW, O'Connell JB, Herskowitz A, et al., for the Myocarditis Treatment Trial Investigators. A clinical trial of immunosuppressive therapy for myocarditis. N Engl J Med. 1995;333:269–75.
56. Mason JW, Bristow MR, Billingham ME, et al. Invasive and noninvasive methods of assessing adriamycin cardiotoxic effects in man: superiority of histopathologic assessment using endomyocardial biopsy. Cancer Treat Rep. 1978;62:857–64.
57. Alexander J, Dainiak N, Berger HJ, et al. Serial assessment of doxorubicin cardiotoxicity with quantitative radionuclide angiocardiography. N Engl J Med. 1979;300:278–83.
58. Cooper LT Jr., Berry GJ, Shabetai R. Idiopathic giant-cell myocarditis—natural history and treatment. Multicenter Giant Cell Myocarditis Study Group Investigators. N Engl J Med. 1997;336: 1860–6.
59. Cesario D, Clark J, Maisel A. Beneficial effects of intermittent home administration of the inotrope/vasodilator milrinone in patients with end-stage congestive heart failure: a preliminary study. Am Heart J. 1998;135:121–9.
60. Leier CV, Binkley PF. Parenteral inotropic support for advanced congestive heart failure. Prog Cardiovasc Dis. 1998;41:207–24.
61. Marius-Nunez AL, Heaney L, Fernandez RN, et al. Intermittent inotropic therapy in an outpatient setting: a cost-effective therapeutic modality in patients with refractory heart failure. Am Heart J. 1996;132:805–8.
62. Drazner MH, Hamilton MA, Fonarow G, et al. Relationship between right and left-sided filling pressures in 1000 patients with advanced heart failure. J Heart Lung Transplant. 1999;18:1126–32.
63. Androne AS, Katz SD, Lund L, et al. Hemodilution is common in patients with advanced heart failure. Circulation. 2003;107:226–9.
64. Tang WH, Girod JP, Lee MJ, et al. Plasma B-type natriuretic peptide levels in ambulatory patients with established chronic symptomatic systolic heart failure. Circulation. 2003;108:2964–6.
65. Mahdyoon H, Klein R, Eyler W, et al. Radiographic pulmonary congestion in end-stage congestive heart failure. Am J Cardiol. 1989;63:625–7.
66. Aaronson KD, Schwartz JS, Chen TM, et al. Development and prospective validation of a clinical index to predict survival in ambulatory patients referred for cardiac transplant evaluation. Circulation. 1997;95:2660–7.
67. Levy WC, Mozaffarian D, Linker DT, et al. The Seattle Heart Failure Model: prediction of survival in heart failure. Circulation. 2006;113:1424–33.
68. Butler J, Khadim G, Paul KM, et al. Selection of patients for heart transplantation in the current era of heart failure therapy. J Am Coll Cardiol. 2004;43:787–93.
69. Zipes DP, Camm AJ, Borggrefe M, et al. ACC/AHA/ESC 2006 guidelines for management of patients with ventricular arrhythmias and the prevention of sudden cardiac death: a report of the American College of Cardiology/American Heart Association Task Force and the European Society of Cardiology Committee for Practice Guidelines (Writing Committee to Develop Guidelines for Management of Patients With Ventricular Arrhythmias and the Prevention of Sudden Cardiac Death). J Am Coll Cardiol. 2006;48:e247–346.
70. Levy D, Larson MG, Vasan RS, et al. The progression from hypertension to congestive heart failure. JAMA. 1996;275:1557–62.
71. Wilhelmsen L, Rosengren A, Eriksson H, et al. Heart failure in the general population of men—morbidity, risk factors and prognosis. J Intern Med. 2001;249:253–61.
72. Effects of treatment on morbidity in hypertension. II. Results in patients with diastolic blood pressure averaging 90 through 114 mm Hg. JAMA. 1970;213:1143–52.
73. Kostis JB, Davis BR, Cutler J, et al., for the SHEP Cooperative Research Group. Prevention of heart failure by antihypertensive drug treatment in older persons with isolated systolic hypertension. JAMA. 1997;278:212–6.
74. Izzo JL Jr., Gradman AH. Mechanisms and management of hypertensive heart disease: from left ventricular hypertrophy to heart failure. Med Clin North Am. 2004;88:1257–71.
75. Baker DW. Prevention of heart failure. J Card Fail. 2002;8:333–46.

76. Vasan RS, Beiser A, Seshadri S, et al. Residual lifetime risk for developing hypertension in middle-aged women and men: The Framingham Heart Study. JAMA. 2002;287:1003–10.
77. Vakili BA, Okin PM, Devereux RB. Prognostic implications of left ventricular hypertrophy. Am Heart J. 2001;141:334–41.
78. Chobanian AV, Bakris GL, Black HR, et al. Seventh report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure. Hypertension. 2003;42:1206–52.
79. Hansson L, Zanchetti A, Carruthers SG, et al., for the HOT Study Group. Effects of intensive blood-pressure lowering and low-dose aspirin in patients with hypertension: principal results of the Hypertension Optimal Treatment (HOT) randomised trial. Lancet. 1998; 351:1755–62.
80. UK Prospective Diabetes Study Group. Tight blood pressure control and risk of macrovascular and microvascular complications in type 2 diabetes: UKPDS 38 [published erratum appears in BMJ 1999;318: 29]. BMJ. 1998;317:703–13.
81. Staessen JA, Wang JG, Thijs L. Cardiovascular protection and blood pressure reduction: a meta-analysis. Lancet. 2001;358:1305–15.
82. Major outcomes in high-risk hypertensive patients randomized to angiotensin-converting enzyme inhibitor or calcium channel blocker vs diuretic: The Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT). JAMA. 2002;288:2981–97.
83. Yusuf S, Sleight P, Pogue J, et al., for the The Heart Outcomes Prevention Evaluation Study Investigators. Effects of an angiotensin-converting-enzyme inhibitor, ramipril, on cardiovascular events in high-risk patients. N Engl J Med. 2000;342:145–53.
84. Fox KM. Efficacy of perindopril in reduction of cardiovascular events among patients with stable coronary artery disease: randomised, double-blind, placebo-controlled, multicentre trial (the EUROPA study). Lancet. 2003;362:782–8.
85. Brenner BM, Cooper ME, de Zeeuw D, et al. Effects of losartan on renal and cardiovascular outcomes in patients with type 2 diabetes and nephropathy. N Engl J Med. 2001;345:861–9.
86. Berl T, Hunsicker LG, Lewis JB, et al. Cardiovascular outcomes in the Irbesartan Diabetic Nephropathy Trial of patients with type 2 diabetes and overt nephropathy. Ann Intern Med. 2003;138:542–9.
87. Smith SC Jr., Blair SN, Bonow RO, et al. AHA/ACC Scientific Statement: AHA/ACC guidelines for preventing heart attack and death in patients with atherosclerotic cardiovascular disease: 2001 update: a statement for healthcare professionals from the American Heart Association and the American College of Cardiology. Circulation. 2001;104:1577–9.
88. Taegtmeyer H, McNulty P, Young ME. Adaptation and maladaptation of the heart in diabetes: Part I: general concepts. Circulation. 2002;105:1727–33.
89. Kenchaiah S, Evans JC, Levy D, et al. Obesity and the risk of heart failure. N Engl J Med. 2002;347:305–13.
90. He J, Ogden LG, Bazzano LA, et al. Risk factors for congestive heart failure in US men and women: NHANES I epidemiologic follow-up study. Arch Intern Med. 2001;161:996–1002.
91. Krumholz HM, Chen YT, Wang Y, et al. Predictors of readmission among elderly survivors of admission with heart failure. Am Heart J. 2000;139:72–7.
92. Shindler DM, Kostis JB, Yusuf S, et al. Diabetes mellitus, a predictor of morbidity and mortality in the Studies of Left Ventricular Dysfunction (SOLVD) Trials and Registry. Am J Cardiol. 1996;77: 1017–20.
93. Vaur L, Gueret P, Lievre M, et al. Development of congestive heart failure in type 2 diabetic patients with microalbuminuria or proteinuria: observations from the DIABHYCAR (type 2 DIABetes, Hypertension, CArdiovascular Events and Ramipril) study. Diabetes Care. 2003;26:855–60.
94. Heart Outcomes Prevention Evaluation Study Investigators. Effects of ramipril on cardiovascular and microvascular outcomes in people with diabetes mellitus: results of the HOPE study and MICRO-HOPE substudy. Lancet. 2000;355:253–9.
95. Kasiske BL, Kalil RS, Ma JZ, et al. Effect of antihypertensive therapy on the kidney in patients with diabetes: a meta-regression analysis. Ann Intern Med. 1993;118:129–38.
96. Lewis EJ, Hunsicker LG, Bain RP, et al., for the Collaborative Study Group. The effect of angiotensin-converting-enzyme inhibition on diabetic nephropathy. N Engl J Med. 1993;329:1456–62.
97. Zanella MT, Ribeiro AB. The role of angiotensin II antagonism in type 2 diabetes mellitus: a review of renoprotection studies. Clin Ther. 2002;24:1019–34.
98. Kereiakes DJ, Willerson JT. Metabolic syndrome epidemic. Circulation. 2003;108:1552–3.
99. Wilson PW, Grundy SM. The metabolic syndrome: practical guide to origins and treatment: Part I. Circulation. 2003;108:1422–4.
100. Grundy SM, Cleeman JI, Merz CN, et al. Implications of recent clinical trials for the National Cholesterol Education Program Adult Treatment Panel III Guidelines. J Am Coll Cardiol. 2004;44: 720–32.
101. Braunwald E, Domanski MJ, Fowler SE, et al. Angiotensin-converting-enzyme inhibition in stable coronary artery disease. N Engl J Med. 2004;351:2058–68.
102. Kjekshus J, Pedersen TR, Olsson AG, et al. The effects of simvastatin on the incidence of heart failure in patients with coronary heart disease [published erratum appears in J Card Fail 1998;4:367]. J Card Fail. 1997;3:249–54.
103. Lewis SJ, Moye LA, Sacks FM, et al. Effect of pravastatin on cardiovascular events in older patients with myocardial infarction and cholesterol levels in the average range. Results of the Cholesterol and Recurrent Events (CARE) trial. Ann Intern Med. 1998;129:681–9.
104. The Long-Term Intervention with Pravastatin in Ischaemic Disease (LIPID) Study Group. Prevention of cardiovascular events and death with pravastatin in patients with coronary heart disease and a broad range of initial cholesterol levels. N Engl J Med. 1998;339:1349–57.
105. Walsh CR, Larson MG, Evans JC, et al. Alcohol consumption and risk for congestive heart failure in the Framingham Heart Study. Ann Intern Med. 2002;136:181–91.
106. Abramson JL, Williams SA, Krumholz HM, et al. Moderate alcohol consumption and risk of heart failure among older persons. JAMA. 2001;285:1971–7.
107. Vallebona A. Cardiac damage following therapeutic chest irradiation. Importance, evaluation and treatment. Minerva Cardioangiol. 2000; 48:79–87.
108. Pai VB, Nahata MC. Cardiotoxicity of chemotherapeutic agents: incidence, treatment and prevention. Drug Saf. 2000;22:263–302.
109. Sparano JA. Cardiac toxicity of trastuzumab (Herceptin): implications for the design of adjuvant trials. Semin Oncol. 2001;28:20–7.
110. Schimmel KJ, Richel DJ, van den Brink RB, et al. Cardiotoxicity of cytotoxic drugs. Cancer Treat Rev. 2004;30:181–91.
111. Soni MG, Carabin IG, Griffiths JC, et al. Safety of ephedra: lessons learned. Toxicol Lett. 2004;150:97–110.
112. Vasan RS, Benjamin EJ, Larson MG, et al. Plasma natriuretic peptides for community screening for left ventricular hypertrophy and systolic dysfunction: the Framingham heart study. JAMA. 2002;288: 1252–9.
113. Heidenreich PA, Gubens MA, Fonarow GC, et al. Cost-effectiveness of screening with B-type natriuretic peptide to identify patients with reduced left ventricular ejection fraction. J Am Coll Cardiol. 2004;43:1019–26.
114. McMinn TR Jr., Ross J Jr. Hereditary dilated cardiomyopathy. Clin Cardiol. 1995;18:7–15.
115. Sung RY, Huang GY, Shing MK, et al. Echocardiographic evaluation of cardiac function in paediatric oncology patients treated with or without anthracycline. Int J Cardiol. 1997;60:239–48.
116. Flather MD, Yusuf S, Kober L, et al., for the ACE-Inhibitor Myocardial Infarction Collaborative Group. Long-term ACE-inhibitor therapy in patients with heart failure or left-ventricular dysfunction: a systematic overview of data from individual patients. Lancet. 2000;355:1575–81.
117. The SOLVD Investigators. Effect of enalapril on mortality and the development of heart failure in asymptomatic patients with reduced left ventricular ejection fractions. [published erratum appears in N Engl J Med 1992;327:1768]. N Engl J Med. 1992;327:685–91.
118. Pitt B, Williams G, Remme W, et al. The EPHESUS trial: eplerenone in patients with heart failure due to systolic dysfunction complicating acute myocardial infarction. Eplerenone Post-AMI Heart Failure Efficacy and Survival Study. Cardiovasc Drugs Ther. 2001;15:79–87.
119. McMurray J, Kober L, Robertson M, et al. Antiarrhythmic effect of carvedilol after acute myocardial infarction: results of the Carvedilol Post-Infarct Survival Control in Left Ventricular Dysfunction (CAPRICORN) trial. J Am Coll Cardiol. 2005;45:525–30.

120. Leon AS, Franklin BA, Costa F, et al. Cardiac rehabilitation and secondary prevention of coronary heart disease: an American Heart Association scientific statement from the Council on Clinical Cardiology (Subcommittee on Exercise, Cardiac Rehabilitation, and Prevention) and the Council on Nutrition, Physical Activity, and Metabolism (Subcommittee on Physical Activity), in collaboration with the American Association of Cardiovascular and Pulmonary Rehabilitation. Circulation. 2005;111:369–76.
121. Guerci AD, Gerstenblith G, Brinker JA, et al. A randomized trial of intravenous tissue plasminogen activator for acute myocardial infarction with subsequent randomization to elective coronary angioplasty. N Engl J Med. 1987;317:1613–8.
122. Gruppo Italiano per lo Studio della Streptochinasi nell'Infarto Miocardico (GISSI). Effectiveness of intravenous thrombolytic treatment in acute myocardial infarction. Lancet. 1986;1:397–402.
123. Gruppo Italiano per lo Studio della Sopravvivenza nell'Infarto Miocardico. GISSI-3: effects of lisinopril and transdermal glyceryl trinitrate singly and together on 6-week mortality and ventricular function after acute myocardial infarction. Lancet. 1994;343:1115–22.
124. Timolol-induced reduction in mortality and reinfarction in patients surviving acute myocardial infarction. N Engl J Med. 1981;304:801–7.
125. Beta Blocker Heart Attack Trial Research Group. A randomized trial of propranolol in patients with acute myocardial infarction. I. Mortality results. JAMA. 1982;247:1707–14.
126. The Acute Infarction Ramipril Efficacy (AIRE) Study Investigators. Effect of ramipril on mortality and morbidity of survivors of acute myocardial infarction with clinical evidence of heart failure. Lancet. 1993;342:821–8.
127. Chadda K, Goldstein S, Byington R, et al. Effect of propranolol after acute myocardial infarction in patients with congestive heart failure. Circulation. 1986;73:503–10.
128. Pfeffer MA, Braunwald E, Moye LA, et al., for the SAVE Investigators. Effect of captopril on mortality and morbidity in patients with left ventricular dysfunction after myocardial infarction. Results of the survival and ventricular enlargement trial. N Engl J Med. 1992;327:669–77.
129. ISIS-4 (Fourth International Study of Infarct Survival) Collaborative Group. ISIS-4: a randomised factorial trial assessing early oral captopril, oral mononitrate, and intravenous magnesium sulphate in 58,050 patients with suspected acute myocardial infarction. Lancet. 1995;345:669–85.
130. Pfeffer MA, McMurray JJ, Velazquez EJ, et al. Valsartan, captopril, or both in myocardial infarction complicated by heart failure, left ventricular dysfunction, or both. N Engl J Med. 2003;349:1893–906.
131. Vantrimpont P, Rouleau JL, Wun CC, et al., for the SAVE Investigators. Additive beneficial effects of beta-blockers to angiotensin-converting enzyme inhibitors in the Survival and Ventricular Enlargement (SAVE) Study. J Am Coll Cardiol. 1997;29:229–36.
132. Jong P, Yusuf S, Rousseau MF, et al. Effect of enalapril on 12–year survival and life expectancy in patients with left ventricular systolic dysfunction: a follow-up study. Lancet. 2003;361:1843–8.
133. Desai AS, Fang JC, Maisel WH, et al. Implantable defibrillators for the prevention of mortality in patients with nonischemic cardiomyopathy: a meta-analysis of randomized controlled trials. JAMA. 2004;292:2874–9.
134. The Digitalis Investigation Group. The effect of digoxin on mortality and morbidity in patients with heart failure. N Engl J Med. 1997;336:525–33.
135. The Multicenter Diltiazem Postinfarction Trial Research Group. The effect of diltiazem on mortality and reinfarction after myocardial infarction. N Engl J Med. 1988;319:385–92.
136. Peters KG, Kienzle MG. Severe cardiomyopathy due to chronic rapidly conducted atrial fibrillation: complete recovery after restoration of sinus rhythm. Am J Med. 1988;85:242–4.
137. Grogan M, Smith HC, Gersh BJ, et al. Left ventricular dysfunction due to atrial fibrillation in patients initially believed to have idiopathic dilated cardiomyopathy. Am J Cardiol. 1992;69:1570–3.
138. Bonow RO, Carabello B, de Leon A Jr., et al. Guidelines for the management of patients with valvular heart disease: executive summary. A report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (Committee on Management of Patients with Valvular Heart Disease). Circulation. 1998;98:1949–84.
139. Bach DS, Bolling SF. Improvement following correction of secondary mitral regurgitation in end-stage cardiomyopathy with mitral annuloplasty. Am J Cardiol. 1996;78:966–9.
140. Connolly HM, Oh JK, Orszulak TA, et al. Aortic valve replacement for aortic stenosis with severe left ventricular dysfunction. Prognostic indicators. Circulation. 1997;95:2395–400.
141. Bolling SF, Pagani FD, Deeb GM, et al. Intermediate-term outcome of mitral reconstruction in cardiomyopathy. J Thorac Cardiovasc Surg. 1998;115:381–6.
142. Greenberg B, Massie B, Bristow JD, et al. Long-term vasodilator therapy of chronic aortic insufficiency. A randomized double-blinded, placebo-controlled clinical trial. Circulation. 1988;78:92–103.
143. Scognamiglio R, Rahimtoola SH, Fasoli G, et al. Nifedipine in asymptomatic patients with severe aortic regurgitation and normal left ventricular function. N Engl J Med. 1994;331:689–94.
144. Epstein AE, DiMarco JP, Ellenbogen KA, et al. ACC/AHA/HRS 2008 Guidelines for Device-Based Therapy of Cardiac Rhythm Abnormalities: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (Writing Committee to Revise the ACC/AHA/NASPE 2002 Guideline Update for Implantation of Cardiac Pacemakers and Antiarrhythmia Devices) developed in collaboration with the American Association for Thoracic Surgery and Society of Thoracic Surgeons. J Am Coll Cardiol. 2008;51:e1–62.
145. Captopril Multicenter Research Group. A placebo-controlled trial of captopril in refractory chronic congestive heart failure. J Am Coll Cardiol. 1983;2:755–63.
146. Garg R, Yusuf S, for the Collaborative Group on ACE Inhibitor Trials. Overview of randomized trials of angiotensin-converting enzyme inhibitors on mortality and morbidity in patients with heart failure. JAMA. 1995;273:1450–6.
147. Sharpe DN, Murphy J, Coxon R, et al. Enalapril in patients with chronic heart failure: a placebo-controlled, randomized, double-blind study. Circulation. 1984;70:271–8.
148. Chalmers JP, West MJ, Cyran J, et al. Placebo-controlled study of lisinopril in congestive heart failure: a multicentre study. J Cardiovasc Pharmacol. 1987;9 Suppl 3:S89–97.
149. Cleland JG, Dargie HJ, Hodsman GP, et al. Captopril in heart failure. A double blind controlled trial. Br Heart J. 1984;52:530–5.
150. Cleland JG, Dargie HJ, Ball SG, et al. Effects of enalapril in heart failure: a double blind study of effects on exercise performance, renal function, hormones, and metabolic state. Br Heart J. 1985;54:305–12.
151. Cowley AJ, Rowley JM, Stainer KL, et al. Captopril therapy for heart failure. A placebo controlled study. Lancet. 1982;2:730–2.
152. Bayliss J, Norell MS, Canepa-Anson R, et al. Clinical importance of the renin-angiotensin system in chronic heart failure: double blind comparison of captopril and prazosin. Br Med J (Clin Res Ed). 1985;290:1861–5.
153. Drexler H, Banhardt U, Meinertz T, et al. Contrasting peripheral short-term and long-term effects of converting enzyme inhibition in patients with congestive heart failure. A double-blind, placebo-controlled trial. Circulation. 1989;79:491–502.
154. Erhardt L, MacLean A, Ilgenfritz J, et al., for the Fosinopril Efficacy/Safety Trial (FEST) Study Group. Fosinopril attenuates clinical deterioration and improves exercise tolerance in patients with heart failure. Eur Heart J. 1995;16:1892–9.
155. The CONSENSUS Trial Study Group. Effects of enalapril on mortality in severe congestive heart failure. Results of the Cooperative North Scandinavian Enalapril Survival Study (CONSENSUS). N Engl J Med. 1987;316:1429–35.
156. Cohn JN, Johnson G, Ziesche S, et al. A comparison of enalapril with hydralazine-isosorbide dinitrate in the treatment of chronic congestive heart failure. N Engl J Med. 1991;325:303–10.
157. The SOLVD Investigators. Effect of enalapril on survival in patients with reduced left ventricular ejection fractions and congestive heart failure. N Engl J Med. 1991;325:293–302.
158. CIBIS-II Investigators and Committee. The Cardiac Insufficiency Bisoprolol Study II (CIBIS-II): a randomised trial. Lancet. 1999;353:9–13.
159. Hjalmarson A, Goldstein S, Fagerberg B, et al., for the MERIT-HF Study Group. Effects of controlled-release metoprolol on total

mortality, hospitalizations, and well-being in patients with heart failure: the Metoprolol CR/XL Randomized Intervention Trial in congestive heart failure (MERIT-HF). JAMA. 2000;283:1295–302.
160. A trial of the beta-blocker bucindolol in patients with advanced chronic heart failure. N Engl J Med. 2001;344:1659–67.
161. Poole-Wilson PA, Swedberg K, Cleland JG, et al. Comparison of carvedilol and metoprolol on clinical outcomes in patients with chronic heart failure in the Carvedilol Or Metoprolol European Trial (COMET): randomised controlled trial. Lancet. 2003;362:7–13.
162. Effect of metoprolol CR/XL in chronic heart failure: Metoprolol CR/XL Randomised Intervention Trial in Congestive Heart Failure (MERIT-HF). Lancet. 1999;353:2001–7.
163. Lechat P, Packer M, Chalon S, et al. Clinical effects of beta-adrenergic blockade in chronic heart failure: a meta-analysis of double-blind, placebo-controlled, randomized trials. Circulation. 1998;98:1184–91.
164. Packer M, Bristow MR, Cohn JN, et al., for the U.S. Carvedilol Heart Failure Study Group. The effect of carvedilol on morbidity and mortality in patients with chronic heart failure. N Engl J Med. 1996;334:1349–55.
165. Packer M, Coats AJ, Fowler MB, et al. Effect of carvedilol on survival in severe chronic heart failure. N Engl J Med. 2001;344:1651–8.
166. Dargie HJ. Effect of carvedilol on outcome after myocardial infarction in patients with left-ventricular dysfunction: the CAPRICORN randomised trial. Lancet. 2001;357:1385–90.
167. Cleland JG, Pennell DJ, Ray SG, et al. Myocardial viability as a determinant of the ejection fraction response to carvedilol in patients with heart failure (CHRISTMAS trial): randomised controlled trial. Lancet. 2003;362:14–21.
168. Fisher ML, Gottlieb SS, Plotnick GD, et al. Beneficial effects of metoprolol in heart failure associated with coronary artery disease: a randomized trial. J Am Coll Cardiol. 1994;23:943–50.
169. Metra M, Nardi M, Giubbini R, et al. Effects of short- and long-term carvedilol administration on rest and exercise hemodynamic variables, exercise capacity and clinical conditions in patients with idiopathic dilated cardiomyopathy. J Am Coll Cardiol. 1994; 24:1678–87.
170. Olsen SL, Gilbert EM, Renlund DG, et al. Carvedilol improves left ventricular function and symptoms in chronic heart failure: a double-blind randomized study. J Am Coll Cardiol. 1995;25:1225–31.
171. Krum H, Sackner-Bernstein JD, Goldsmith RL, et al. Double-blind, placebo-controlled study of the long-term efficacy of carvedilol in patients with severe chronic heart failure. Circulation. 1995;92:1499–506.
172. Waagstein F, Bristow MR, Swedberg K, et al., for the Metoprolol in Dilated Cardiomyopathy (MDC) Trial Study Group. Beneficial effects of metoprolol in idiopathic dilated cardiomyopathy. Lancet. 1993;342:1441–6.
173. CIBIS Investigators and Committees. A randomized trial of beta-blockade in heart failure. The Cardiac Insufficiency Bisoprolol Study (CIBIS). Circulation. 1994;90:1765–73.
174. Packer M, Colucci WS, Sackner-Bernstein JD, et al. Double-blind, placebo-controlled study of the effects of carvedilol in patients with moderate to severe heart failure. The PRECISE Trial. Prospective Randomized Evaluation of Carvedilol on Symptoms and Exercise. Circulation. 1996;94:2793–9.
175. Colucci WS, Packer M, Bristow MR, et al., for the US Carvedilol Heart Failure Study Group. Carvedilol inhibits clinical progression in patients with mild symptoms of heart failure. Circulation. 1996;94: 2800–6.
176. Australia/New Zealand Heart Failure Research Collaborative Group. Randomised, placebo-controlled trial of carvedilol in patients with congestive heart failure due to ischaemic heart disease. Lancet. 1997;349:375–80.
177. Granger CB, McMurray JJ, Yusuf S, et al. Effects of candesartan in patients with chronic heart failure and reduced left-ventricular systolic function intolerant to angiotensin-converting-enzyme inhibitors: the CHARM-Alternative trial. Lancet. 2003;362:772–6.
178. Gottlieb SS, Dickstein K, Fleck E, et al. Hemodynamic and neurohormonal effects of the angiotensin II antagonist losartan in patients with congestive heart failure. Circulation. 1993;88:1602–9.
179. Crozier I, Ikram H, Awan N, et al., for the Losartan Hemodynamic Study Group. Losartan in heart failure. Hemodynamic effects and tolerability. Circulation. 1995;91:691–7.
180. Riegger GA, Bouzo H, Petr P, et al., for the Symptom, Tolerability, Response to Exercise Trial of Candesartan Cilexetil in Heart Failure (STRETCH) Investigators. Improvement in exercise tolerance and symptoms of congestive heart failure during treatment with candesartan cilexetil. Circulation. 1999;100:2224–30.
181. Sharma D, Buyse M, Pitt B, et al., for the Losartan Heart Failure Mortality Meta-analysis Study Group. Meta-analysis of observed mortality data from all-controlled, double-blind, multiple-dose studies of losartan in heart failure. Am J Cardiol. 2000;85:187–92.
182. McKelvie RS, Yusuf S, Pericak D, et al., for the RESOLVD Pilot Study Investigators. Comparison of candesartan, enalapril, and their combination in congestive heart failure: randomized evaluation of strategies for left ventricular dysfunction (RESOLVD) pilot study. Circulation. 1999;100:1056–64.
183. Mazayev VP, Fomina IG, Kazakov EN, et al. Valsartan in heart failure patients previously untreated with an ACE inhibitor. Int J Cardiol. 1998;65:239–46.
184. Cohn JN, Tognoni G. A randomized trial of the angiotensin-receptor blocker valsartan in chronic heart failure. N Engl J Med. 2001;345:1667–75.
185. Wong M, Staszewsky L, Latini R, et al. Valsartan benefits left ventricular structure and function in heart failure: Val-HeFT echocardiographic study. J Am Coll Cardiol. 2002;40:970–5.
186. McMurray JJ, Ostergren J, Swedberg K, et al. Effects of candesartan in patients with chronic heart failure and reduced left-ventricular systolic function taking angiotensin-converting-enzyme inhibitors: the CHARM-Added trial. Lancet. 2003;362:767–71.
187. Heerdink ER, Leufkens HG, Herings RM, et al. NSAIDs associated with increased risk of congestive heart failure in elderly patients taking diuretics. Arch Intern Med. 1998;158:1108–12.
188. Herchuelz A, Derenne F, Deger F, et al. Interaction between nonsteroidal anti-inflammatory drugs and loop diuretics: modulation by sodium balance. J Pharmacol Exp Ther. 1989;248:1175–81.
189. Gottlieb SS, Robinson S, Krichten CM, et al. Renal response to indomethacin in congestive heart failure secondary to ischemic or idiopathic dilated cardiomyopathy. Am J Cardiol. 1992;70:890–3.
190. Bank AJ, Kubo SH, Rector TS, et al. Local forearm vasodilation with intra-arterial administration of enalaprilat in humans. Clin Pharmacol Ther. 1991;50:314–21.
191. The Cardiac Arrhythmia Suppression Trial (CAST) Investigators. Preliminary report: effect of encainide and flecainide on mortality in a randomized trial of arrhythmia suppression after myocardial infarction. N Engl J Med. 1989;321:406–12.
192. The Cardiac Arrhythmia Suppression Trial II Investigators. Effect of the antiarrhythmic agent moricizine on survival after myocardial infarction. N Engl J Med. 1992;327:227–33.
193. Pratt CM, Eaton T, Francis M, et al. The inverse relationship between baseline left ventricular ejection fraction and outcome of antiarrhythmic therapy: a dangerous imbalance in the risk-benefit ratio. Am Heart J. 1989;118:433–40.
193a. Nilsson BB, Westheim A, Risberg MA. Effects of group-based high-intensity aerobic interval training in patients with chronic heart failure. Am J Cardiol. 2008;102:1361–5.
193b. Mueller L, Myers J, Kottman W, et al. Exercise capacity, physical activity patterns and outcomes six years after cardiac rehabilitation in patients with heart failure. Clin Rehabil. 2007;21:923–31.
193c. Dracup K, Evangelista LS, Hamilton MA, et al. Effects of a home-based exercise program on clinical outcomes in heart failure. Am Heart J. 2007;154:877–83.
193d. Jónsdóttir S, Andersen KK, Sigurosson AF, Sigurosson SB. The effect of physical training in chronic heart failure. Eur J Heart Fail. 2006;8:97–101.
194. Bokhari F, Newman D, Greene M, et al. Long-term comparison of the implantable cardioverter defibrillator versus amiodarone: eleven-year follow-up of a subset of patients in the Canadian Implantable Defibrillator Study (CIDS). Circulation. 2004;110:112–6.
195. Mark DB, Nelson CL, Anstrom KJ, et al. Cost-effectiveness of defibrillator therapy or amiodarone in chronic stable heart failure: results from the Sudden Cardiac Death in Heart Failure Trial (SCD-HeFT). Circulation. 2006;114:135–42.
196. Bardy GH, Lee KL, Mark DB, et al. Amiodarone or an implantable cardioverter-defibrillator for congestive heart failure. N Engl J Med. 2005;352:225–37.

197. Hebert K, McKinnie J, Horswell R, et al. Expansion of heart failure device therapy into a rural indigent population in Louisiana: potential economic and health policy implications. J Card Fail. 2006;12: 689–93.
198. Knight BP, Goyal R, Pelosi F, et al. Outcome of patients with nonischemic dilated cardiomyopathy and unexplained syncope treated with an implantable defibrillator. J Am Coll Cardiol. 1999; 33:1964–70.
199. Klein HU, Reek S. The MUSTT study: evaluating testing and treatment. J Interv Card Electrophysiol. 2000;4 Suppl 1:45–50.
200. Moss AJ, Zareba W, Hall WJ, et al. Prophylactic implantation of a defibrillator in patients with myocardial infarction and reduced ejection fraction. N Engl J Med. 2002;346:877–83.
201. Hohnloser SH, Connolly SJ, Kuck KH, et al. The defibrillator in acute myocardial infarction trial (DINAMIT): study protocol. Am Heart J. 2000;140:735–9.
202. Wilkoff BL, Cook JR, Epstein AE, et al. Dual-chamber pacing or ventricular backup pacing in patients with an implantable defibrillator: the Dual Chamber and VVI Implantable Defibrillator (DAVID) Trial. JAMA. 2002;288:3115–23.
203. Beshai JF, Grimm RA, Nagueh SF, et al. Cardiac-resynchronization therapy in heart failure with narrow QRS complexes. N Engl J Med. 2007;357:2461–71.
204. Cleland JG, Daubert JC, Erdmann E, et al. The effect of cardiac resynchronization on morbidity and mortality in heart failure. N Engl J Med. 2005;352:1539–49.
205. Higgins SL, Hummel JD, Niazi IK, et al. Cardiac resynchronization therapy for the treatment of heart failure in patients with intraventricular conduction delay and malignant ventricular tachyarrhythmias. J Am Coll Cardiol. 2003;42:1454–9.
206. Xiao HB, Roy C, Fujimoto S, et al. Natural history of abnormal conduction and its relation to prognosis in patients with dilated cardiomyopathy. Int J Cardiol. 1996;53:163–70.
207. Shamim W, Francis DP, Yousufuddin M, et al. Intraventricular conduction delay: a prognostic marker in chronic heart failure. Int J Cardiol. 1999;70:171–8.
208. Unverferth DV, Magorien RD, Moeschberger ML, et al. Factors influencing the one-year mortality of dilated cardiomyopathy. Am J Cardiol. 1984;54:147–52.
209. Blanc JJ, Etienne Y, Gilard M, et al. Evaluation of different ventricular pacing sites in patients with severe heart failure: results of an acute hemodynamic study. Circulation. 1997;96:3273–7.
210. Kass DA, Chen CH, Curry C, et al. Improved left ventricular mechanics from acute VDD pacing in patients with dilated cardiomyopathy and ventricular conduction delay. Circulation. 1999;99: 1567–73.
211. Toussaint JF, Lavergne T, Ollitraut J, et al. Biventricular pacing in severe heart failure patients reverses electromechanical dyssynchronization from apex to base. Pacing Clin Electrophysiol. 2000;23: 1731–4.
212. Nelson GS, Berger RD, Fetics BJ, et al. Left ventricular or biventricular pacing improves cardiac function at diminished energy cost in patients with dilated cardiomyopathy and left bundle-branch block. Circulation. 2000;102:3053–9.
213. Abraham WT, Fisher WG, Smith AL, et al. Cardiac resynchronization in chronic heart failure. N Engl J Med. 2002;346:1845–53.
214. Young JB, Abraham WT, Smith AL, et al. Combined cardiac resynchronization and implantable cardioversion defibrillation in advanced chronic heart failure: the MIRACLE ICD Trial. JAMA. 2003;289:2685–94.
215. McAlister FA, Stewart S, Ferrua S, et al. Multidisciplinary strategies for the management of heart failure patients at high risk for admission: a systematic review of randomized trials. J Am Coll Cardiol. 2004;44:810–9.
216. Bristow MR, Saxon LA, Boehmer J, et al. Cardiac-resynchronization therapy with or without an implantable defibrillator in advanced chronic heart failure. N Engl J Med. 2004;350:2140–50.
217. Leclercq C, Walker S, Linde C, et al. Comparative effects of permanent biventricular and right-univentricular pacing in heart failure patients with chronic atrial fibrillation. Eur Heart J. 2002;23: 1780–7.
218. Leon AR, Greenberg JM, Kanuru N, et al. Cardiac resynchronization in patients with congestive heart failure and chronic atrial fibrillation: effect of upgrading to biventricular pacing after chronic right ventricular pacing. J Am Coll Cardiol. 2002;39:1258–63.
219. Juurlink DN, Mamdani M, Kopp A, et al. Drug-drug interactions among elderly patients hospitalized for drug toxicity. JAMA. 2003; 289:1652–8.
220. Juurlink DN, Mamdani MM, Lee DS, et al. Rates of hyperkalemia after publication of the Randomized Aldactone Evaluation Study. N Engl J Med. 2004;351:543–51.
221. Svensson M, Gustafsson F, Galatius S, et al. How prevalent is hyperkalemia and renal dysfunction during treatment with spironolactone in patients with congestive heart failure? J Card Fail. 2004;10:297–303.
222. Carson P, Ziesche S, Johnson G, et al., for the Vasodilator-Heart Failure Trial Study Group. Racial differences in response to therapy for heart failure: analysis of the vasodilator-heart failure trials. J Card Fail. 1999;5:178–87.
223. Taylor AL, Ziesche S, Yancy C, et al. Combination of isosorbide dinitrate and hydralazine in blacks with heart failure. N Engl J Med. 2004;351:2049–57.
224. Stevenson WG, Tedrow U. Management of atrial fibrillation in patients with heart failure. Heart Rhythm. 2007;4:S28–30.
225. Heist EK, Ruskin JN. Atrial fibrillation and congestive heart failure: risk factors, mechanisms, and treatment. Prog Cardiovasc Dis. 2006;48:256–69.
226. Roy D, Talajic M, Nattel S, et al. Rhythm control versus rate control for atrial fibrillation and heart failure. N Engl J Med. 2008;358: 2667–77.
227. Wyse DG, Waldo AL, DiMarco JP, et al. A comparison of rate control and rhythm control in patients with atrial fibrillation. N Engl J Med. 2002;347:1825–33.
228. Van Gelder I, Hagens VE, Bosker HA, et al. A comparison of rate control and rhythm control in patients with recurrent persistent atrial fibrillation. N Engl J Med. 2002;347:1834–40.
229. The Captopril-Digoxin Multicenter Research Group. Comparative effects of therapy with captopril and digoxin in patients with mild to moderate heart failure. JAMA. 1988;259:539–44.
230. Dobbs SM, Kenyon WI, Dobbs RJ. Maintenance digoxin after an episode of heart failure: placebo-controlled trial in outpatients. Br Med J. 1977;1:749–52.
231. Lee DC, Johnson RA, Bingham JB, et al. Heart failure in outpatients: a randomized trial of digoxin versus placebo. N Engl J Med. 1982;306:699–705.
232. Guyatt GH, Sullivan MJ, Fallen EL, et al. A controlled trial of digoxin in congestive heart failure. Am J Cardiol. 1988;61:371–5.
233. DiBianco R, Shabetai R, Kostuk W, et al. A comparison of oral milrinone, digoxin, and their combination in the treatment of patients with chronic heart failure. N Engl J Med. 1989;320:677–83.
234. Uretsky BF, Young JB, Shahidi FE, et al., for the PROVED Investigative Group. Randomized study assessing the effect of digoxin withdrawal in patients with mild to moderate chronic congestive heart failure: results of the PROVED trial. J Am Coll Cardiol. 1993;22:955–62.
235. Packer M, Gheorghiade M, Young JB, et al. Withdrawal of digoxin from patients with chronic heart failure treated with angiotensin-converting-enzyme inhibitors. RADIANCE Study. N Engl J Med. 1993;329:1–7.
236. Cohn JN. The Vasodilator-Heart Failure Trials (V-HeFT). Mechanistic data from the VA Cooperative Studies. Introduction. Circulation. 1993;87:VI1–4.
237. Cazeau S, Leclercq C, Lavergne T, et al. Effects of multisite biventricular pacing in patients with heart failure and intraventricular conduction delay. N Engl J Med. 2001;344:873–80.
238. Cohn JN, Archibald DG, Ziesche S, et al. Effect of vasodilator therapy on mortality in chronic congestive heart failure. Results of a Veterans Administration Cooperative Study. N Engl J Med. 1986; 314:1547–52.
239. Loeb HS, Johnson G, Henrick A, et al., for the V-HeFT VA Cooperative Studies Group. Effect of enalapril, hydralazine plus isosorbide dinitrate, and prazosin on hospitalization in patients with chronic congestive heart failure. Circulation. 1993;87:VI78–87.
240. Reed SD, Friedman JY, Velazquez EJ, et al. Multinational economic evaluation of valsartan in patients with chronic heart failure: results from the Valsartan Heart Failure Trial (Val-HeFT). Am Heart J. 2004;148:122–8.

241. Setaro JF, Zaret BL, Schulman DS, et al. Usefulness of verapamil for congestive heart failure associated with abnormal left ventricular diastolic filling and normal left ventricular systolic performance. Am J Cardiol. 1990;66:981–6.
242. Packer M, O'Connor CM, Ghali JK, et al., for the Prospective Randomized Amlodipine Survival Evaluation Study Group. Effect of amlodipine on morbidity and mortality in severe chronic heart failure. N Engl J Med. 1996;335:1107–14.
243. McKelvie RS, Teo KK, McCartney N, et al. Effects of exercise training in patients with congestive heart failure: a critical review. J Am Coll Cardiol. 1995;25:789–96.
244. Chati Z, Zannad F, Jeandel C, et al. Physical deconditioning may be a mechanism for the skeletal muscle energy phosphate metabolism abnormalities in chronic heart failure. Am Heart J. 1996;131:560–6.
245. Sinoway LI. Effect of conditioning and deconditioning stimuli on metabolically determined blood flow in humans and implications for congestive heart failure. Am J Cardiol. 1988;62:45E–8E.
246. Mancini DM, Walter G, Reichek N, et al. Contribution of skeletal muscle atrophy to exercise intolerance and altered muscle metabolism in heart failure. Circulation. 1992;85:1364–73.
247. Packer M. Hemodynamic consequences of antiarrhythmic drug therapy in patients with chronic heart failure. J Cardiovasc Electrophysiol. 1991;2:S240–7.
248. Torp-Pedersen C, Moller M, Bloch-Thomsen PE, et al., for the Danish Investigations of Arrhythmia and Mortality on Dofetilide Study Group. Dofetilide in patients with congestive heart failure and left ventricular dysfunction. N Engl J Med. 1999;341:857–65.
249. Packer M, Kessler PD, Lee WH. Calcium-channel blockade in the management of severe chronic congestive heart failure: a bridge too far. Circulation. 1987;75:V56–64.
250. Elkayam U. Calcium channel blockers in heart failure. Cardiology. 1998;89 Suppl 1:38–46.
251. Packer M, Gottlieb SS, Kessler PD. Hormone-electrolyte interactions in the pathogenesis of lethal cardiac arrhythmias in patients with congestive heart failure. Basis of a new physiologic approach to control of arrhythmia. Am J Med. 1986;80:23–9.
252. Packer M. Adaptive and maladaptive actions of angiotensin II in patients with severe congestive heart failure. Am J Kidney Dis. 1987;10:66–73.
253. Reid JL, Whyte KF, Struthers AD. Epinephrine-induced hypokalemia: the role of beta adrenoceptors. Am J Cardiol. 1986;57:23F–7F.
254. Packer M. Potential role of potassium as a determinant of morbidity and mortality in patients with systemic hypertension and congestive heart failure. Am J Cardiol. 1990;65:45E–51E.
255. Schwartz AB. Potassium-related cardiac arrhythmias and their treatment. Angiology. 1978;29:194–205.
256. Pitt B, Zannad F, Remme WJ, et al., for the Randomized Aldactone Evaluation Study Investigators. The effect of spironolactone on morbidity and mortality in patients with severe heart failure. N Engl J Med. 1999;341:709–17.
257. Rude RK. Physiology of magnesium metabolism and the important role of magnesium in potassium deficiency. Am J Cardiol. 1989;63:31G–4G.
258. Rich MW, Beckham V, Wittenberg C, et al. A multidisciplinary intervention to prevent the readmission of elderly patients with congestive heart failure. N Engl J Med. 1995;333:1190–5.
259. Shah NB, Der E, Ruggerio C, et al. Prevention of hospitalizations for heart failure with an interactive home monitoring program. Am Heart J. 1998;135:373–8.
260. Fonarow GC, Stevenson LW, Walden JA, et al. Impact of a comprehensive heart failure management program on hospital readmission and functional status of patients with advanced heart failure. J Am Coll Cardiol. 1997;30:725–32.
261. Philbin EF. Comprehensive multidisciplinary programs for the management of patients with congestive heart failure. J Gen Intern Med. 1999;14:130–5.
262. Packer M, Cohn JN, Abraham WT, et al. Consensus recommendations for the management of chronic heart failure. Am J Cardiol. 1999;83:1A–38A.
263. Brater DC. Diuretic therapy. N Engl J Med. 1998;339:387–95.
264. Cody RJ, Kubo SH, Pickworth KK. Diuretic treatment for the sodium retention of congestive heart failure. Arch Intern Med. 1994;154:1905–14.
265. Patterson JH, Adams KF Jr., Applefeld MM, et al., for the Torsemide Investigators Group. Oral torsemide in patients with chronic congestive heart failure: effects on body weight, edema, and electrolyte excretion. Pharmacotherapy. 1994;14:514–21.
266. Sherman LG, Liang CS, Baumgardner S, et al. Piretanide, a potent diuretic with potassium-sparing properties, for the treatment of congestive heart failure. Clin Pharmacol Ther. 1986;40:587–94.
267. Wilson JR, Reichek N, Dunkman WB, et al. Effect of diuresis on the performance of the failing left ventricle in man. Am J Med. 1981;70:234–9.
268. Parker JO, for the The Ibopamine Study Group. The effects of oral ibopamine in patients with mild heart failure—a double blind placebo controlled comparison to furosemide. Int J Cardiol. 1993;40:221–7.
269. Richardson A, Bayliss J, Scriven AJ, et al. Double-blind comparison of captopril alone against frusemide plus amiloride in mild heart failure. Lancet. 1987;2:709–11.
270. Packer M, Medina N, Yushak M, et al. Hemodynamic patterns of response during long-term captopril therapy for severe chronic heart failure. Circulation. 1983;68:803–12.
271. Hall SA, Cigarroa CG, Marcoux L, et al. Time course of improvement in left ventricular function, mass and geometry in patients with congestive heart failure treated with beta-adrenergic blockade. J Am Coll Cardiol. 1995;25:1154–61.
272. Cody RJ, Franklin KW, Laragh JH. Postural hypotension during tilt with chronic captopril and diuretic therapy of severe congestive heart failure. Am Heart J. 1982;103:480–4.
273. Massie B, Kramer B, Haughom F. Postural hypotension and tachycardia during hydralazine–isosorbide dinitrate therapy for chronic heart failure. Circulation. 1981;63:658–64.
274. Packer M, Lee WH, Medina N, et al. Functional renal insufficiency during long-term therapy with captopril and enalapril in severe chronic heart failure. Ann Intern Med. 1987;106:346–54.
275. Risler T, Schwab A, Kramer B, et al. Comparative pharmacokinetics and pharmacodynamics of loop diuretics in renal failure. Cardiology. 1994;84 Suppl 2:155–61.
276. Murray MD, Forthofer MM, Bennett SK, et al. Effectiveness of torsemide and furosemide in the treatment of congestive heart failure: results of a prospective, randomized trial (abstr). Circulation. 1999;100 Suppl 1:I-300.
277. Cody RJ, Covit AB, Schaer GL, et al. Sodium and water balance in chronic congestive heart failure. J Clin Invest. 1986;77:1441–52.
278. Vasko MR, Cartwright DB, Knochel JP, et al. Furosemide absorption altered in decompensated congestive heart failure. Ann Intern Med. 1985;102:314–8.
279. Brater DC, Chennavasin P, Seiwell R. Furosemide in patients with heart failure: shift in dose-response curves. Clin Pharmacol Ther. 1980;28:182–6.
280. Vargo DL, Kramer WG, Black PK, et al. Bioavailability, pharmacokinetics, and pharmacodynamics of torsemide and furosemide in patients with congestive heart failure. Clin Pharmacol Ther. 1995;57:601–9.
281. Brater DC, Harris C, Redfern JS, et al. Renal effects of cox-2–selective inhibitors. Am J Nephrol. 2001;21:1–15.
282. Dormans TP, van Meyel JJ, Gerlag PG, et al. Diuretic efficacy of high dose furosemide in severe heart failure: bolus injection versus continuous infusion. J Am Coll Cardiol. 1996;28:376–82.
283. Epstein M, Lepp BA, Hoffman DS, et al. Potentiation of furosemide by metolazone in refractory edema. Curr Ther Res. 1977;21:656–67.
284. Sica DA, Gehr TW. Diuretic combinations in refractory oedema states: pharmacokinetic-pharmacodynamic relationships. Clin Pharmacokinet. 1996;30:229–49.
285. Ellison DH. The physiologic basis of diuretic synergism: its role in treating diuretic resistance. Ann Intern Med. 1991;114:886–94.
286. Oster JR, Epstein M, Smoller S. Combined therapy with thiazide-type and loop diuretic agents for resistant sodium retention. Ann Intern Med. 1983;99:405–6.
287. Steiness E, Olesen KH. Cardiac arrhythmias induced by hypokalaemia and potassium loss during maintenance digoxin therapy. Br Heart J. 1976;38:167–72.
288. Solomon R. The relationship between disorders of K+ and Mg+ homeostasis. Semin Nephrol. 1987;7:253–62.
289. Feigenbaum MS, Welsch MA, Mitchell M, et al. Contracted plasma and blood volume in chronic heart failure. J Am Coll Cardiol. 2000;35:51–5.

290. Swartz SL, Williams GH, Hollenberg NK, et al. Captopril-induced changes in prostaglandin production: relationship to vascular responses in normal man. J Clin Invest. 1980;65:1257–64.
291. Brown NJ, Ryder D, Gainer JV, et al. Differential effects of angiotensin converting enzyme inhibitors on the vasodepressor and prostacyclin responses to bradykinin. J Pharmacol Exp Ther. 1996; 279:703–12.
292. Gainer JV, Morrow JD, Loveland A, et al. Effect of bradykinin-receptor blockade on the response to angiotensin-converting-enzyme inhibitor in normotensive and hypertensive subjects. N Engl J Med. 1998;339:1285–92.
293. Linz W, Scholkens BA. A specific B2–bradykinin receptor antagonist HOE 140 abolishes the antihypertrophic effect of ramipril. Br J Pharmacol. 1992;105:771–2.
294. McDonald KM, Garr M, Carlyle PF, et al. Relative effects of alpha 1-adrenoceptor blockade, converting enzyme inhibitor therapy, and angiotensin II subtype 1 receptor blockade on ventricular remodeling in the dog. Circulation. 1994;90:3034–46.
295. McDonald KM, Mock J, D'Aloia A, et al. Bradykinin antagonism inhibits the antigrowth effect of converting enzyme inhibition in the dog myocardium after discrete transmural myocardial necrosis. Circulation. 1995;91:2043–8.
296. Bastien NR, Juneau AV, Ouellette J, et al. Chronic AT1 receptor blockade and angiotensin-converting enzyme (ACE) inhibition in (CHF 146) cardiomyopathic hamsters: effects on cardiac hypertrophy and survival. Cardiovasc Res. 1999;43:77–85.
297. Pitt B, Poole-Wilson PA, Segal R, et al. Effect of losartan compared with captopril on mortality in patients with symptomatic heart failure: randomised trial—the Losartan Heart Failure Survival Study ELITE II. Lancet. 2000;355:1582–7.
298. The NETWORK Investigators. Clinical outcome with enalapril in symptomatic chronic heart failure; a dose comparison. Eur Heart J. 1998;19:481–9.
299. Massie BM, Armstrong PW, Cleland JG, et al. Toleration of high doses of angiotensin-converting enzyme inhibitors in patients with chronic heart failure: results from the ATLAS trial. The Assessment of Treatment with Lisinopril and Survival. Arch Intern Med. 2001;161:165–71.
300. Pflugfelder PW, Baird MG, Tonkon MJ, et al., for the Quinapril Heart Failure Trial Investigators. Clinical consequences of angiotensin-converting enzyme inhibitor withdrawal in chronic heart failure: a double-blind, placebo-controlled study of quinapril. J Am Coll Cardiol. 1993;22:1557–63.
301. Cleland JG, Gillen G, Dargie HJ. The effects of frusemide and angiotensin-converting enzyme inhibitors and their combination on cardiac and renal haemodynamics in heart failure. Eur Heart J. 1988;9:132–41.
302. Flapan AD, Davies E, Waugh C, et al. Acute administration of captopril lowers the natriuretic and diuretic response to a loop diuretic in patients with chronic cardiac failure. Eur Heart J. 1991;12:924–7.
303. Hall D, Zeitler H, Rudolph W. Counteraction of the vasodilator effects of enalapril by aspirin in severe heart failure. J Am Coll Cardiol. 1992;20:1549–55.
304. Kindsvater S, Leclerc K, Ward J. Effects of coadministration of aspirin or clopidogrel on exercise testing in patients with heart failure receiving angiotensin-converting enzyme inhibitors. Am J Cardiol. 2003;91:1350–2.
305. Spaulding C, Charbonnier B, Cohen-Solal A, et al. Acute hemodynamic interaction of aspirin and ticlopidine with enalapril: results of a double-blind, randomized comparative trial. Circulation. 1998;98: 757–65.
306. Al Khadra AS, Salem DN, Rand WM, et al. Antiplatelet agents and survival: a cohort analysis from the Studies of Left Ventricular Dysfunction (SOLVD) trial. J Am Coll Cardiol. 1998;31:419–25.
307. Nguyen KN, Aursnes I, Kjekshus J. Interaction between enalapril and aspirin on mortality after acute myocardial infarction: subgroup analysis of the Cooperative New Scandinavian Enalapril Survival Study II (CONSENSUS II). Am J Cardiol. 1997;79:115–9.
308. Teo KK, Yusuf S, Pfeffer M, et al. Effects of long-term treatment with angiotensin-converting-enzyme inhibitors in the presence or absence of aspirin: a systematic review. Lancet. 2002;360:1037–43.
309. Harjai KJ, Solis S, Prasad A, et al. Use of aspirin in conjunction with angiotensin-converting enzyme inhibitors does not worsen long-term survival in heart failure. Int J Cardiol. 2003;88:207–14.
310. Antiplatelet Trialists' Collaboration. Collaborative overview of randomised trials of antiplatelet therapy—I: prevention of death, myocardial infarction, and stroke by prolonged antiplatelet therapy in various categories of patients. [published erratum appears in BMJ 1994;308:1540]. BMJ. 1994;308:81–106.
311. Jones CG, Cleland JG. Meeting report—the LIDO, HOPE, MOXCON and WASH studies. Heart Outcomes Prevention Evaluation. The Warfarin/Aspirin Study of Heart Failure. Eur J Heart Fail. 1999;1:425–31.
312. CAPRIE Steering Committee. A randomised, blinded, trial of clopidogrel versus aspirin in patients at risk of ischaemic events (CAPRIE). Lancet. 1996;348:1329–39.
313. Packer M, Medina N, Yushak M. Relation between serum sodium concentration and the hemodynamic and clinical responses to converting enzyme inhibition with captopril in severe heart failure. J Am Coll Cardiol. 1984;3:1035–43.
314. Packer M, Lee WH, Kessler PD. Preservation of glomerular filtration rate in human heart failure by activation of the renin-angiotensin system. Circulation. 1986;74:766–74.
315. Packer M, Lee WH, Kessler PD, et al. Identification of hyponatremia as a risk factor for the development of functional renal insufficiency during converting enzyme inhibition in severe chronic heart failure. J Am Coll Cardiol. 1987;10:837–44.
316. Hasenfuss G, Holubarsch C, Blanchard EM, et al. Influence of isoproterenol on myocardial energetics. Experimental and clinical investigations. Basic Res Cardiol. 1989;84 Suppl 1:147–55.
317. Giles TD, Katz R, Sullivan JM, et al., for the Multicenter Lisinopril-Captopril Congestive Heart Failure Study Group. Short- and long-acting angiotensin-converting enzyme inhibitors: a randomized trial of lisinopril versus captopril in the treatment of congestive heart failure. J Am Coll Cardiol. 1989;13:1240–7.
318. Burnier M, Waeber B, Nussberger J, et al. Effect of angiotensin converting enzyme inhibition in renovascular hypertension. J Hypertens. 1989;7 Suppl:S27–31.
319. Packer M, Lee WH, Medina N, et al. Influence of diabetes mellitus on changes in left ventricular performance and renal function produced by converting enzyme inhibition in patients with severe chronic heart failure. Am J Med. 1987;82:1119–26.
320. Israili ZH, Hall WD. Cough and angioneurotic edema associated with angiotensin-converting enzyme inhibitor therapy. A review of the literature and pathophysiology. Ann Intern Med. 1992;117:234–42.
321. Woo KS, Nicholls MG. High prevalence of persistent cough with angiotensin converting enzyme inhibitors in Chinese. Br J Clin Pharmacol. 1995;40:141–4.
322. Cicardi M, Zingale LC, Bergamaschini L, et al. Angioedema associated with angiotensin-converting enzyme inhibitor use: outcome after switching to a different treatment. Arch Intern Med. 2004;164:910–3.
323. Warner KK, Visconti JA, Tschampel MM. Angiotensin II receptor blockers in patients with ACE inhibitor-induced angioedema. Ann Pharmacother. 2000;34:526–8.
324. Fuchs SA, Meyboom RH, van Puijenbroek EP, et al. Use of angiotensin receptor antagonists in patients with ACE inhibitor induced angioedema. Pharm World Sci. 2004;26:191–2.
325. Struthers AD. Angiotensin II receptor antagonists for heart failure [editorial]. Heart. 1998;80:5–6.
326. Packer M, Kessler PD, Gottlieb SS. Adverse effects of converting-enzyme inhibition in patients with severe congestive heart failure: pathophysiology and management. Postgrad Med J. 1986;62 Suppl 1:179–82.
327. Yusuf S, Pfeffer MA, Swedberg K, et al. Effects of candesartan in patients with chronic heart failure and preserved left-ventricular ejection fraction: the CHARM-Preserved Trial. Lancet. 2003;362: 777–81.
328. Struthers AD. Aldosterone escape during angiotensin-converting enzyme inhibitor therapy in chronic heart failure. J Card Fail. 1996;2:47–54.
329. Hensen J, Abraham WT, Durr JA, et al. Aldosterone in congestive heart failure: analysis of determinants and role in sodium retention. Am J Nephrol. 1991;11:441–6.

330. Duprez DA, De Buyzere ML, Rietzschel ER, et al. Inverse relationship between aldosterone and large artery compliance in chronically treated heart failure patients. Eur Heart J. 1998;19:1371–6.
331. Rocha R, Chander PN, Khanna K, et al. Mineralocorticoid blockade reduces vascular injury in stroke-prone hypertensive rats. Hypertension. 1998;31:451–8.
332. MacFadyen RJ, Barr CS, Struthers AD. Aldosterone blockade reduces vascular collagen turnover, improves heart rate variability and reduces early morning rise in heart rate in heart failure patients. Cardiovasc Res. 1997;35:30–4.
333. Barr CS, Lang CC, Hanson J, et al. Effects of adding spironolactone to an angiotensin-converting enzyme inhibitor in chronic congestive heart failure secondary to coronary artery disease. Am J Cardiol. 1995;76:1259–65.
334. Weber KT, Villarreal D. Aldosterone and antialdosterone therapy in congestive heart failure. Am J Cardiol. 1993;71:3A–11A.
335. Zannad F. Aldosterone and heart failure. Eur Heart J. 1995;16 Suppl N:98–102.
335a. Pitt B, Remme W, Zannad F, et al. Eplerenone, a selective aldosterone blocker, in patients with left ventricular dysfunction after myocardial infarction. N Engl J Med. 2003;348:1309–21.
336. Smith KM, Macmillan JB, McGrath JC. Investigation of alpha1-adrenoceptor subtypes mediating vasoconstriction in rabbit cutaneous resistance arteries. Br J Pharmacol. 1997;122:825–32.
337. Elhawary AM, Pang CC. Alpha 1b-adrenoceptors mediate renal tubular sodium and water reabsorption in the rat. Br J Pharmacol. 1994;111:819–24.
338. Simons M, Downing SE. Coronary vasoconstriction and catecholamine cardiomyopathy. Am Heart J. 1985;109:297–304.
339. Knowlton KU, Michel MC, Itani M, et al. The alpha 1A-adrenergic receptor subtype mediates biochemical, molecular, and morphologic features of cultured myocardial cell hypertrophy. J Biol Chem. 1993;268:15374–80.
340. Molina-Viamonte V, Anyukhovsky EP, Rosen MR. An alpha-1-adrenergic receptor subtype is responsible for delayed afterdepolarizations and triggered activity during simulated ischemia and reperfusion of isolated canine Purkinje fibers. Circulation. 1991;84:1732–40.
341. Kaumann AJ, Sanders L. Both beta 1- and beta 2-adrenoceptors mediate catecholamine-evoked arrhythmias in isolated human right atrium. Naunyn Schmiedebergs Arch Pharmacol. 1993;348:536–40.
342. Billman GE, Castillo LC, Hensley J, et al. Beta2-adrenergic receptor antagonists protect against ventricular fibrillation: in vivo and in vitro evidence for enhanced sensitivity to beta2-adrenergic stimulation in animals susceptible to sudden death. Circulation. 1997;96:1914–22.
343. Communal C, Singh K, Pimentel DR, et al. Norepinephrine stimulates apoptosis in adult rat ventricular myocytes by activation of the beta-adrenergic pathway. Circulation. 1998;98:1329–34.
344. Xamoterol in severe heart failure. The Xamoterol in Severe Heart Failure Study Group. Lancet. 1990;336:1–6.[published erratum appears in Lancet 1990;336:698]
345. Packer M, Coats AJS, Fowler MB, et al. Effect of carvedilol on the survival of patients with severe chronic heart failure. N Engl J Med. 2001;344:1651–8.
346. Packer M, Coats AJ, Fowler MB, et al. Effect of carvedilol on survival in severe chronic heart failure. N Engl J Med. 2001;344:1651–8.
347. Packer M, Poole-Wilson PA, Armstrong PW, et al., for the ATLAS Study Group. Comparative effects of low and high doses of the angiotensin-converting enzyme inhibitor, lisinopril, on morbidity and mortality in chronic heart failure. Circulation. 1999;100:2312–8.
348. Epstein SE, Braunwald E. The effect of beta adrenergic blockade on patterns of urinary sodium excretion. Studies in normal subjects and in patients with heart disease. Ann Intern Med. 1966;65:20–7.
349. Weil JV, Chidsey CA. Plasma volume expansion resulting from interference with adrenergic function in normal man. Circulation. 1968;37:54–61.
350. Gaffney TE, Braunwald E. Importance of the adrenergic nervous system in the support of circulatory function in patients with congestive heart failure. Am J Med. 2000;34:320–4.
351. Gattis WA, O'Connor CM, Gallup DS, et al. Predischarge initiation of carvedilol in patients hospitalized for decompensated heart failure: results of the Initiation Management Predischarge: Process for Assessment of Carvedilol Therapy in Heart Failure (IMPACT-HF) trial. J Am Coll Cardiol. 2004;43:1534–41.
352. Waagstein F, Caidahl K, Wallentin I, et al. Long-term beta-blockade in dilated cardiomyopathy. Effects of short- and long-term metoprolol treatment followed by withdrawal and readministration of metoprolol. Circulation. 1989;80:551–63.
353. Gattis WA, O'Connor CM, Leimberger JD, et al. Clinical outcomes in patients on beta-blocker therapy admitted with worsening chronic heart failure. Am J Cardiol. 2003;91:169–74.
354. MERIT-HF Study Group. Effects of metoprolol CR in patients with ischemic and dilated cardiomyopathy: the randomized evaluation of strategies for left ventricular dysfunction pilot study. Circulation. 2000;101:378–84.
355. Akera T, Baskin SI, Tobin T, et al. Ouabain: temporal relationship between the inotropic effect and the in vitro binding to, and dissociation from, (Na++K+)-activated ATPase. Naunyn Schmiedebergs Arch Pharmacol. 1973;277:151–62.
356. Thames MD. Acetylstrophanthidin-induced reflex inhibition of canine renal sympathetic nerve activity mediated by cardiac receptors with vagal afferents. Circ Res. 1979;44:8–15.
357. Ferguson DW, Berg WJ, Sanders JS, et al. Sympathoinhibitory responses to digitalis glycosides in heart failure patients. Direct evidence from sympathetic neural recordings. Circulation. 1989;80:65–77.
358. Torretti J, Hendler E, Weinstein E, et al. Functional significance of Na-K-ATPase in the kidney: effects of ouabain inhibition. Am J Physiol. 1972;222:1398–405.
359. Covit AB, Schaer GL, Sealey JE, et al. Suppression of the renin-angiotensin system by intravenous digoxin in chronic congestive heart failure. Am J Med. 1983;75:445–7.
360. Gheorghiade M, Ferguson D. Digoxin. A neurohormonal modulator in heart failure? Circulation. 1991;84:2181–6.
361. Gheorghiade M, Adams KF Jr., Colucci WS. Digoxin in the management of cardiovascular disorders. Circulation. 2004;109:2959–64.
362. Rahimtoola SH. Digitalis therapy for patients in clinical heart failure. Circulation. 2004;109:2942–6.
363. Matsuda M, Matsuda Y, Yamagishi T, et al. Effects of digoxin, propranolol, and verapamil on exercise in patients with chronic isolated atrial fibrillation. Cardiovasc Res. 1991;25:453–7.
364. David D, Segni ED, Klein HO, et al. Inefficacy of digitalis in the control of heart rate in patients with chronic atrial fibrillation: beneficial effect of an added beta adrenergic blocking agent. Am J Cardiol. 1979;44:1378–82.
365. Farshi R, Kistner D, Sarma JS, et al. Ventricular rate control in chronic atrial fibrillation during daily activity and programmed exercise: a crossover open-label study of five drug regimens. J Am Coll Cardiol. 1999;33:304–10.
366. Khand AU, Rankin AC, Martin W, et al. Carvedilol alone or in combination with digoxin for the management of atrial fibrillation in patients with heart failure? J Am Coll Cardiol. 2003;42:1944–51.
367. Jelliffe RW, Brooker G. A nomogram for digoxin therapy. Am J Med. 1974;57:63–8.
368. Adams KF Jr., Gheorghiade M, Uretsky BF, et al. Clinical benefits of low serum digoxin concentrations in heart failure. J Am Coll Cardiol. 2002;39:946–53.
369. Rathore SS, Curtis JP, Wang Y, et al. Association of serum digoxin concentration and outcomes in patients with heart failure. JAMA. 2003;289:871–8.
370. Steiner JF, Robbins LJ, Hammermeister KE, et al. Incidence of digoxin toxicity in outpatients. West J Med. 1994;161:474–8.
371. Arnold SB, Byrd RC, Meister W, et al. Long-term digitalis therapy improves left ventricular function in heart failure. N Engl J Med. 1980;303:1443–8.
372. Gheorghiade M, Hall VB, Jacobsen G, et al. Effects of increasing maintenance dose of digoxin on left ventricular function and neurohormones in patients with chronic heart failure treated with diuretics and angiotensin-converting enzyme inhibitors. Circulation. 1995;92:1801–7.
373. Slatton ML, Irani WN, Hall SA, et al. Does digoxin provide additional hemodynamic and autonomic benefit at higher doses in patients with mild to moderate heart failure and normal sinus rhythm? J Am Coll Cardiol. 1997;29:1206–13.
374. Fogelman AM, La Mont JT, Finkelstein S, et al. Fallibility of plasma-digoxin in differentiating toxic from non-toxic patients. Lancet. 1971;2:727–9.

375. Ingelfinger JA, Goldman P. The serum digitalis concentration—does it diagnose digitalis toxicity? N Engl J Med. 1976;294:867–70.
376. Hager WD, Fenster P, Mayersohn M, et al. Digoxin-quinidine interaction Pharmacokinetic evaluation. N Engl J Med. 1979;300: 1238–41.
377. Bizjak ED, Mauro VF. Digoxin-macrolide drug interaction. Ann Pharmacother. 1997;31:1077–9.
378. Hedman A. Inhibition by basic drugs of digoxin secretion into human bile. Eur J Clin Pharmacol. 1992;42:457–9.
379. Rathore SS, Wang Y, Krumholz HM. Sex-based differences in the effect of digoxin for the treatment of heart failure. N Engl J Med. 2002;347:1403–11.
380. Leor J, Goldbourt U, Rabinowitz B, et al., for the SPRINT Study Group. Digoxin and increased mortality among patients recovering from acute myocardial infarction: importance of digoxin dose. Cardiovasc Drugs Ther. 1995;9:723–9.
381. Eichhorn EJ, Gheorghiade M. Digoxin. Prog Cardiovasc Dis. 2002;44:251–66.
382. Uretsky BF, Thygesen K, Armstrong PW, et al. Acute coronary findings at autopsy in heart failure patients with sudden death: results from the assessment of treatment with lisinopril and survival (ATLAS) trial. Circulation. 2000;102:611–6.
383. Luu M, Stevenson WG, Stevenson LW, et al. Diverse mechanisms of unexpected cardiac arrest in advanced heart failure. Circulation. 1989;80:1675–80.
384. Packer M. Sudden unexpected death in patients with congestive heart failure: a second frontier. Circulation. 1985;72:681–5.
385. Kjekshus J. Arrhythmias and mortality in congestive heart failure. Am J Cardiol. 1990;65:42I–8I.
386. Packer M. Lack of relation between ventricular arrhythmias and sudden death in patients with chronic heart failure. Circulation. 1992;85:I50–6.
387. Twidale N, McDonald T, Nave K, et al. Comparison of the effects of AV nodal ablation versus AV nodal modification in patients with congestive heart failure and uncontrolled atrial fibrillation. Pacing Clin Electrophysiol. 1998;21:641–51.
388. Coplen SE, Antman EM, Berlin JA, et al. Efficacy and safety of quinidine therapy for maintenance of sinus rhythm after cardioversion. A meta-analysis of randomized control trials [published erratum appears in Circulation 1991;83:714]. Circulation. 1990;82:1106–16.
389. Waldo AL, Camm AJ, deRuyter H, et al., for the SWORD Investigators. Effect of d-sotalol on mortality in patients with left ventricular dysfunction after recent and remote myocardial infarction. Survival With Oral d-Sotalol [published erratum appears in Lancet 1996 Aug 10;348(9024):416]. Lancet. 1996;348:7–12.
390. Pratt CM, Camm AJ, Cooper W, et al. Mortality in the Survival With ORal D-sotalol (SWORD) trial: why did patients die? Am J Cardiol. 1998;81:869–76.
391. Du XJ, Esler MD, Dart AM. Sympatholytic action of intravenous amiodarone in the rat heart. Circulation. 1995;91:462–70.
392. Doval HC, Nul DR, Grancelli HO, et al., for the Grupo de Estudio de la Sobrevida en la Insuficiencia Cardiaca en Argentina (GESICA). Randomised trial of low-dose amiodarone in severe congestive heart failure. Lancet. 1994;344:493–8.
393. Singh SN, Fletcher RD, Fisher SG, et al. Amiodarone in patients with congestive heart failure and asymptomatic ventricular arrhythmia. Survival Trial of Antiarrhythmic Therapy in Congestive Heart Failure. N Engl J Med. 1995;333:77–82.
394. Massie BM, Fisher SG, Radford M, et al., for the CHF-STAT Investigators. Effect of amiodarone on clinical status and left ventricular function in patients with congestive heart failure. [published erratum appears in Circulation 1996;94:2668]. Circulation. 1996;93: 2128–34.
395. Kadish A, Dyer A, Daubert JP, et al. Prophylactic defibrillator implantation in patients with nonischemic dilated cardiomyopathy. N Engl J Med. 2004;350:2151–8.
396. Soejima K, Suzuki M, Maisel WH, et al. Catheter ablation in patients with multiple and unstable ventricular tachycardias after myocardial infarction: short ablation lines guided by reentry circuit isthmuses and sinus rhythm mapping. Circulation. 2001;104:664–9.
397. Elkayam U, Johnson JV, Shotan A, et al. Double-blind, placebo-controlled study to evaluate the effect of organic nitrates in patients with chronic heart failure treated with angiotensin-converting enzyme inhibition. Circulation. 1999;99:2652–7.
398. Garg UC, Hassid A. Nitric oxide-generating vasodilators and 8-bromo-cyclic guanosine monophosphate inhibit mitogenesis and proliferation of cultured rat vascular smooth muscle cells. J Clin Invest. 1989;83:1774–7.
399. Calderone A, Thaik CM, Takahashi N, et al. Nitric oxide, atrial natriuretic peptide, and cyclic GMP inhibit the growth-promoting effects of norepinephrine in cardiac myocytes and fibroblasts. J Clin Invest. 1998;101:812–8.
400. Jugdutt BI, Khan MI. Effect of prolonged nitrate therapy on left ventricular remodeling after canine acute myocardial infarction. Circulation. 1994;89:2297–307.
401. Massie B, Chatterjee K, Werner J, et al. Hemodynamic advantage of combined administration of hydralazine orally and nitrates nonparenterally in the vasodilator therapy of chronic heart failure. Am J Cardiol. 1977;40:794–801.
402. Pierpont GL, Cohn JN, Franciosa JA. Combined oral hydralazine-nitrate therapy in left ventricular failure. Hemodynamic equivalency to sodium nitroprusside. Chest. 1978;73:8–13.
403. Dhalla AK, Hill MF, Singal PK. Role of oxidative stress in transition of hypertrophy to heart failure. J Am Coll Cardiol. 1996;28:506–14.
404. Keith M, Geranmayegan A, Sole MJ, et al. Increased oxidative stress in patients with congestive heart failure. J Am Coll Cardiol. 1998; 31:1352–6.
405. Bauer JA, Fung HL. Concurrent hydralazine administration prevents nitroglycerin-induced hemodynamic tolerance in experimental heart failure. Circulation. 1991;84:35–9.
406. Gogia H, Mehra A, Parikh S, et al. Prevention of tolerance to hemodynamic effects of nitrates with concomitant use of hydralazine in patients with chronic heart failure. J Am Coll Cardiol. 1995;26: 1575–80.
407. Watanabe H, Kakihana M, Ohtsuka S, et al. Preventive effects of carvedilol on nitrate tolerance—a randomized, double-blind, placebo-controlled comparative study between carvedilol and arotinolol. J Am Coll Cardiol. 1998;32:1201–6.
408. Watanabe H, Kakihana M, Ohtsuka S, et al. Randomized, double-blind, placebo-controlled study of carvedilol on the prevention of nitrate tolerance in patients with chronic heart failure. J Am Coll Cardiol. 1998;32:1194–200.
409. Silverman ME, Pressel MD, Brackett JC, et al. Prognostic value of the signal-averaged electrocardiogram and a prolonged QRS in ischemic and nonischemic cardiomyopathy. Am J Cardiol. 1995;75: 460–4.
410. Fried AG, Parker AB, Newton GE, et al. Electrical and hemodynamic correlates of the maximal rate of pressure increase in the human left ventricle. J Card Fail. 1999;5:8–16.
411. Wilensky RL, Yudelman P, Cohen AI, et al. Serial electrocardiographic changes in idiopathic dilated cardiomyopathy confirmed at necropsy. Am J Cardiol. 1988;62:276–83.
412. Grines CL, Bashore TM, Boudoulas H, et al. Functional abnormalities in isolated left bundle branch block. The effect of interventricular asynchrony. Circulation. 1989;79:845–53.
413. Xiao HB, Lee CH, Gibson DG. Effect of left bundle branch block on diastolic function in dilated cardiomyopathy. Br Heart J. 1991;66: 443–7.
414. Takeshita A, Basta LL, Kioschos JM. Effect of intermittent left bundle branch block on left ventricular performance. Am J Med. 1974;56:251–5.
415. McDonald CD, Burch GE, Walsh JJ. Prolonged bed rest in the treatment of idiopathic cardiomyopathy. Am J Med. 1972;52:41–50.
416. Hochman JS, Healy B. Effect of exercise on acute myocardial infarction in rats. J Am Coll Cardiol. 1986;7:126–32.
417. Oh BH, Ono S, Rockman HA, et al. Myocardial hypertrophy in the ischemic zone induced by exercise in rats after coronary reperfusion. Circulation. 1993;87:598–607.
418. Jugdutt BI, Michorowski BL, Kappagoda CT. Exercise training after anterior Q wave myocardial infarction: importance of regional left ventricular function and topography. J Am Coll Cardiol. 1988;12: 362–72.
419. North TC, McCullagh P, Tran ZV. Effect of exercise on depression. Exer Sport Sci Rev. 1990;18:379–415.
420. Piepoli MF, Flather M, Coats AJ. Overview of studies of exercise training in chronic heart failure: the need for a prospective randomized multicentre European trial. Eur Heart J. 1998;19:830–41.

421. Coats AJ, Adamopoulos S, Meyer TE, et al. Effects of physical training in chronic heart failure. Lancet. 1990;335:63–6.
422. Hambrecht R, Niebauer J, Fiehn E, et al. Physical training in patients with stable chronic heart failure: effects on cardiorespiratory fitness and ultrastructural abnormalities of leg muscles. J Am Coll Cardiol. 1995;25:1239–49.
423. Meyer K, Schwaibold M, Westbrook S, et al. Effects of exercise training and activity restriction on 6-minute walking test performance in patients with chronic heart failure. Am Heart J. 1997;133:447–53.
424. Kiilavuori K, Toivonen L, Naveri H, et al. Reversal of autonomic derangements by physical training in chronic heart failure assessed by heart rate variability. Eur Heart J. 1995;16:490–5.
425. Kostis JB, Rosen RC, Cosgrove NM, et al. Nonpharmacologic therapy improves functional and emotional status in congestive heart failure. Chest. 1994;106:996–1001.
426. Keteyian SJ, Levine AB, Brawner CA, et al. Exercise training in patients with heart failure. A randomized, controlled trial. Ann Intern Med. 1996;124:1051–7.
427. Meyer TE, Casadei B, Coats AJ, et al. Angiotensin-converting enzyme inhibition and physical training in heart failure. J Intern Med. 1991;230:407–13.
428. Demopoulos L, Yeh M, Gentilucci M, et al. Nonselective beta-adrenergic blockade with carvedilol does not hinder the benefits of exercise training in patients with congestive heart failure. Circulation. 1997;95:1764–7.
429. European Heart Failure Training Group. Experience from controlled trials of physical training in chronic heart failure. Protocol and patient factors in effectiveness in the improvement in exercise tolerance. Eur Heart J. 1998;19:466–75.
430. Belardinelli R, Georgiou D, Cianci G, et al. Randomized, controlled trial of long-term moderate exercise training in chronic heart failure: effects on functional capacity, quality of life, and clinical outcome. Circulation. 1999;99:1173–82.
431. Hambrecht R, Fiehn E, Weigl C, et al. Regular physical exercise corrects endothelial dysfunction and improves exercise capacity in patients with chronic heart failure. Circulation. 1998;98:2709–15.
432. Coats AJ, Adamopoulos S, Radaelli A, et al. Controlled trial of physical training in chronic heart failure. Exercise performance, hemodynamics, ventilation, and autonomic function. Circulation. 1992;85:2119–31.
433. Cooksey JD, Reilly P, Brown S, et al. Exercise training and plasma catecholamines in patients with ischemic heart disease. Am J Cardiol. 1978;42:372–6.
434. Orenstein TL, Parker TG, Butany JW, et al. Favorable left ventricular remodeling following large myocardial infarction by exercise training. Effect on ventricular morphology and gene expression. J Clin Invest. 1995;96:858–66.
435. Wang J, Yi GH, Knecht M, et al. Physical training alters the pathogenesis of pacing-induced heart failure through endothelium-mediated mechanisms in awake dogs. Circulation. 1997;96:2683–92.
436. Naughton MT, Bradley TD. Sleep apnea in congestive heart failure. Clin Chest Med. 1998;19:99–113.
437. Shahar E, Whitney CW, Redline S, et al. Sleep-disordered breathing and cardiovascular disease: cross-sectional results of the Sleep Heart Health Study. Am J Respir Crit Care Med. 2001;163:19–25.
438. Tkacova R, Rankin F, Fitzgerald FS, et al. Effects of continuous positive airway pressure on obstructive sleep apnea and left ventricular afterload in patients with heart failure. Circulation. 1998;98:2269–75.
439. Javaheri S. Effects of continuous positive airway pressure on sleep apnea and ventricular irritability in patients with heart failure. Circulation. 2000;101:392–7.
440. Malone S, Liu PP, Holloway R, et al. Obstructive sleep apnoea in patients with dilated cardiomyopathy: effects of continuous positive airway pressure. Lancet. 1991;338:1480–4.
441. Michaels AD, Accad M, Ports TA, et al. Left ventricular systolic unloading and augmentation of intracoronary pressure and Doppler flow during enhanced external counterpulsation. Circulation. 2002;106:1237–42.
442. Arora RR, Chou TM, Jain D, et al. The multicenter study of enhanced external counterpulsation (MUST-EECP): effect of EECP on exercise-induced myocardial ischemia and anginal episodes. J Am Coll Cardiol. 1999;33:1833–40.
443. Bonetti PO, Barsness GW, Keelan PC, et al. Enhanced external counterpulsation improves endothelial function in patients with symptomatic coronary artery disease. J Am Coll Cardiol. 2003;41:1761–8.
444. Linnemeier G, Rutter MK, Barsness G, et al. Enhanced external counterpulsation for the relief of angina in patients with diabetes: safety, efficacy and 1-year clinical outcomes. Am Heart J. 2003;146:453–8.
445. Soran O, Kennard ED, Kelsey SF, et al. Enhanced external counterpulsation as treatment for chronic angina in patients with left ventricular dysfunction: a report from the International EECP Patient Registry (IEPR). Congest Heart Fail. 2002;8:297–302.
446. Soran O, Fleishman B, DeMarco T, et al. Enhanced external counterpulsation in patients with heart failure: a multicenter feasibility study. Congest Heart Fail. 2002;8:204–8, 227.
447. Goldsmith SR. Congestive heart failure: potential role of arginine vasopressin antagonists in the therapy of heart failure. Congest Heart Fail. 2002;8:251–6.
448. Gheorghiade M, Niazi I, Ouyang J, et al. Vasopressin V2-receptor blockade with tolvaptan in patients with chronic heart failure: results from a double-blind, randomized trial. Circulation. 2003;107:2690–6.
449. Udelson JE, Smith WB, Hendrix GH, et al. Acute hemodynamic effects of conivaptan, a dual V(1A) and V(2) vasopressin receptor antagonist, in patients with advanced heart failure. Circulation. 2001;104:2417–23.
450. Gheorghiade M, Gattis WA, O'Connor CM, et al. Effects of tolvaptan, a vasopressin antagonist, in patients hospitalized with worsening heart failure: a randomized controlled trial. JAMA. 2004;291:1963–71.
451. Russell SD, Selaru P, Pyne DA, et al. Rationale for use of an exercise end point and design for the ADVANCE (A Dose evaluation of a Vasopressin ANtagonist in CHF patients undergoing Exercise) trial. Am Heart J. 2003;145:179–86.
452. Magalski A, Adamson P, Gadler F, et al. Continuous ambulatory right heart pressure measurements with an implantable hemodynamic monitor: a multicenter, 12-month follow-up study of patients with chronic heart failure. J Card Fail. 2002;8:63–70.
453. Adamson PB, Magalski A, Braunschweig F, et al. Ongoing right ventricular hemodynamics in heart failure: clinical value of measurements derived from an implantable monitoring system. J Am Coll Cardiol. 2003;41:565–71.
454. Chaudhry PA, Mishima T, Sharov VG, et al. Passive epicardial containment prevents ventricular remodeling in heart failure. Ann Thorac Surg. 2000;70:1275–80.
455. Raman JS, Hata M, Storer M, et al. The mid-term results of ventricular containment (ACORN WRAP) for end-stage ischemic cardiomyopathy. Ann Thorac Cardiovasc Surg. 2001;7:278–81.
456. Di Donato M, Toso A, Maioli M, et al. Intermediate survival and predictors of death after surgical ventricular restoration. Semin Thorac Cardiovasc Surg. 2001;13:468–75.
457. Menicanti L, Di Donato M. The Dor procedure: what has changed after fifteen years of clinical practice? J Thorac Cardiovasc Surg. 2002;124:886–90.
458. Athanasuleas CL, Stanley AW Jr., Buckberg GD, et al., for the RESTORE Group. Surgical anterior ventricular endocardial restoration (SAVER) in the dilated remodeled ventricle after anterior myocardial infarction. Reconstructive Endoventricular Surgery, returning Torsion Original Radius Elliptical Shape to the LV. J Am Coll Cardiol. 2001;37:1199–209.
459. Colucci WS, Elkayam U, Horton DP, et al., for the Nesiritide Study Group. Intravenous nesiritide, a natriuretic peptide, in the treatment of decompensated congestive heart failure. N Engl J Med. 2000;343:246–53.
460. Elkayam U, Akhter MW, Singh H, et al. Comparison of effects on left ventricular filling pressure of intravenous nesiritide and high-dose nitroglycerin in patients with decompensated heart failure. Am J Cardiol. 2004;93:237–40.
461. Intravenous nesiritide vs nitroglycerin for treatment of decompensated congestive heart failure: a randomized controlled trial. JAMA. 2002;287:1531–40.
462. Sackner-Bernstein JD, Skopicki HA, Aaronson KD. Risk of worsening renal function with nesiritide in patients with acutely decompensated heart failure. Circulation. 2005;111:1487–91.

463. Sackner-Bernstein JD, Kowalski M, Fox M, et al. Short-term risk of death after treatment with nesiritide for decompensated heart failure: a pooled analysis of randomized controlled trials. JAMA. 2005;293:1900–5.
464. Azuma J, Sawamura A, Awata N. Usefulness of taurine in chronic congestive heart failure and its prospective application. Jpn Circ J. 1992;56:95–9.
465. Fazio S, Sabatini D, Capaldo B, et al. A preliminary study of growth hormone in the treatment of dilated cardiomyopathy. N Engl J Med. 1996;334:809–14.
466. Ferrari R, De Giuli F. The propionyl-L-carnitine hypothesis: an alternative approach to treating heart failure. J Card Fail. 1997;3:217–24.
467. Ghatak A, Brar MJ, Agarwal A, et al. Oxy free radical system in heart failure and therapeutic role of oral vitamin E. Int J Cardiol. 1996;57:119–27.
468. Hamilton MA, Stevenson LW. Thyroid hormone abnormalities in heart failure: possibilities for therapy. Thyroid. 1996;6:527–9.
469. Soja AM, Mortensen SA. Treatment of congestive heart failure with coenzyme Q10 illuminated by meta-analyses of clinical trials. Mol Aspects Med. 1997;18 Suppl:S159–68.
470. Morris CD, Carson S. Routine vitamin supplementation to prevent cardiovascular disease: a summary of the evidence for the U.S. Preventive Services Task Force. Ann Intern Med. 2003;139:56–70.
471. Hofman-Bang C, Rehnqvist N, Swedberg K, et al., for the Q10 Study Group. Coenzyme Q10 as an adjunctive in the treatment of chronic congestive heart failure. J Card Fail. 1995;1:101–7.
472. Watson PS, Scalia GM, Galbraith A, et al. Lack of effect of coenzyme Q on left ventricular function in patients with congestive heart failure. J Am Coll Cardiol. 1999;33:1549–52.
473. Baggio E, Gandini R, Plancher AC, et al., for the CoQ10 Drug Surveillance Investigators. Italian multicenter study on the safety and efficacy of coenzyme Q10 as adjunctive therapy in heart failure. Mol Aspects Med. 1994;15 Suppl:s287–94.
474. Miller KL, Liebowitz RS, Newby LK. Complementary and alternative medicine in cardiovascular disease: a review of biologically based approaches. Am Heart J. 2004;147:401–11.
475. Vogel JH, Bolling SF, Costello RB, et al. Integrating complementary medicine into cardiovascular medicine. A report of the American College of Cardiology Foundation Task Force on Clinical Expert Consensus Documents (Writing Committee to Develop an Expert Consensus Document on Complementary and Integrative Medicine). J Am Coll Cardiol. 2005;46:184–221.
476. Anderson JL. Hemodynamic and clinical benefits with intravenous milrinone in severe chronic heart failure: results of a multicenter study in the United States. Am Heart J. 1991;121:1956–64.
477. Hatzizacharias A, Makris T, Krespi P, et al. Intermittent milrinone effect on long-term hemodynamic profile in patients with severe congestive heart failure. Am Heart J. 1999;138:241–6.
478. Cadel A, Brusoni B, Pirelli P, et al. Effects of digoxin, placebo and ibopamine on exercise tolerance and cardiac rhythm of patients with chronic post-infarct left ventricular failure. Arzneimittelforschung. 1986;36:376–9.
479. Colucci WS, Sonnenblick EH, Adams KF, et al., for the Milrinone Multicenter Trials Investigators. Efficacy of phosphodiesterase inhibition with milrinone in combination with converting enzyme inhibitors in patients with heart failure. J Am Coll Cardiol. 1993;22:113A–8A.
480. DiBianco R, Shabetai R, Silverman BD, et al. Oral amrinone for the treatment of chronic congestive heart failure: results of a multicenter randomized double-blind and placebo-controlled withdrawal study. J Am Coll Cardiol. 1984;4:855–66.
481. Glover DR, Wathen CG, Murray RG, et al. Are the clinical benefits of oral prenalterol in ischaemic heart failure due to beta blockade? A six month randomised double blind comparison with placebo. Br Heart J. 1985;53:208–15.
482. Goldberg AD, Nicklas J, Goldstein S, for the Imazodan Research Group. Effectiveness of imazodan for treatment of chronic congestive heart failure. Am J Cardiol. 1991;68:631–6.
483. Massie B, Bourassa M, DiBianco R, et al. Long-term oral administration of amrinone for congestive heart failure: lack of efficacy in a multicenter controlled trial. Circulation. 1985;71:963–71.
484. Narahara KA, for the The Western Enoximone Study Group. Oral enoximone therapy in chronic heart failure: a placebo-controlled randomized trial. Am Heart J. 1991;121:1471–9.
485. Roubin GS, Choong CY, Devenish-Meares S, et al. Beta-adrenergic stimulation of the failing ventricle: a double-blind, randomized trial of sustained oral therapy with prenalterol. Circulation. 1984;69:955–62.
486. Uretsky BF, Jessup M, Konstam MA, et al., for the Enoximone Multicenter Trial Group. Multicenter trial of oral enoximone in patients with moderate to moderately severe congestive heart failure. Lack of benefit compared with placebo. Circulation. 1990;82:774–80.
487. van Veldhuisen DJ, Man in 't Veld AJ, Dunselman PH, et al. Double-blind placebo-controlled study of ibopamine and digoxin in patients with mild to moderate heart failure: results of the Dutch Ibopamine Multicenter Trial (DIMT). J Am Coll Cardiol. 1993;22:1564–73.
488. Weber KT, Andrews V, Janicki JS, et al. Pirbuterol, an oral beta-adrenergic receptor agonist, in the treatment of chronic cardiac failure. Circulation. 1982;66:1262–7.
489. Cohn JN, Goldstein SO, Greenberg BH, et al., for the Vesnarinone Trial Investigators. A dose-dependent increase in mortality with vesnarinone among patients with severe heart failure. N Engl J Med. 1998;339:1810–6.
490. Cowley AJ, Skene AM, for the Enoximone Investigators. Treatment of severe heart failure: quantity or quality of life? A trial of enoximone. Br Heart J. 1994;72:226–30.
491. Feldman AM, Bristow MR, Parmley WW, et al., for the Vesnarinone Study Group. Effects of vesnarinone on morbidity and mortality in patients with heart failure. N Engl J Med. 1993;329:149–55.
492. Hampton JR, van Veldhuisen DJ, Kleber FX, et al., for the Second Prospective Randomised Study of Ibopamine on Mortality and Efficacy (PRIME II) Investigators. Randomised study of effect of ibopamine on survival in patients with advanced severe heart failure. Lancet. 1997;349:971–7.
493. Lubsen J, Just H, Hjalmarsson AC, et al. Effect of pimobendan on exercise capacity in patients with heart failure: main results from the Pimobendan in Congestive Heart Failure (PICO) trial. Heart. 1996;76:223–31.
494. Packer M, Carver JR, Rodeheffer RJ, et al., for the PROMISE Study Research Group. Effect of oral milrinone on mortality in severe chronic heart failure. N Engl J Med. 1991;325:1468–75.
495. Applefeld MM, Newman KA, Sutton FJ, et al. Outpatient dobutamine and dopamine infusions in the management of chronic heart failure: clinical experience in 21 patients. Am Heart J. 1987;114:589–95.
496. Elis A, Bental T, Kimchi O, et al. Intermittent dobutamine treatment in patients with chronic refractory congestive heart failure: a randomized, double-blind, placebo-controlled study. Clin Pharmacol Ther. 1998;63:682–5.
497. Zile MR, Brutsaert DL. New concepts in diastolic dysfunction and diastolic heart failure: Part I: diagnosis, prognosis, and measurements of diastolic function. Circulation. 2002;105:1387–93.
498. Hogg K, Swedberg K, McMurray J. Heart failure with preserved left ventricular systolic function; epidemiology, clinical characteristics, and prognosis. J Am Coll Cardiol. 2004;43:317–27.
499. Aronow WS, Ahn C, Kronzon I. Prognosis of congestive heart failure in elderly patients with normal versus abnormal left ventricular systolic function associated with coronary artery disease. Am J Cardiol. 1990;66:1257–9.
500. Davie AP, Francis CM, Caruana L, et al. The prevalence of left ventricular diastolic filling abnormalities in patients with suspected heart failure. Eur Heart J. 1997;18:981–4.
501. Dougherty AH, Naccarelli GV, Gray EL, et al. Congestive heart failure with normal systolic function. Am J Cardiol. 1984;54:778–82.
502. Iriarte M, Murga N, Sagastagoitia D, et al. Congestive heart failure from left ventricular diastolic dysfunction in systemic hypertension. Am J Cardiol. 1993;71:308–12.
503. Litwin SE, Grossman W. Diastolic dysfunction as a cause of heart failure. J Am Coll Cardiol. 1993;22:49A–55A.
504. Burkhoff D, Maurer MS, Packer M. Heart failure with a normal ejection fraction: is it really a disorder of diastolic function? Circulation. 2003;107:656–8.

505. Brutsaert DL, Sys SU, Gillebert TC. Diastolic failure: pathophysiology and therapeutic implications [published erratum appears in J Am Coll Cardiol. 1993;22:1272]. J Am Coll Cardiol. 1993;22:318–25.
506. Mendes LA, Davidoff R, Cupples LA, et al. Congestive heart failure in patients with coronary artery disease: the gender paradox. Am Heart J. 1997;134:207–12.
507. Senni M, Redfield MM. Heart failure with preserved systolic function. A different natural history? J Am Coll Cardiol. 2001;38:1277–82.
508. Redfield MM. Heart failure—an epidemic of uncertain proportions. N Engl J Med. 2002;347:1442–4.
509. Banerjee P, Banerjee T, Khand A, et al. Diastolic heart failure: neglected or misdiagnosed? J Am Coll Cardiol. 2002;39:138–41.
510. Konstam MA. Systolic and diastolic dysfunction in heart failure? Time for a new paradigm. J Card Fail. 2003;9:1–3.
511. van Kraaij DJ, van Pol PE, Ruiters AW, et al. Diagnosing diastolic heart failure. Eur J Heart Fail. 2002;4:419–30.
512. Vasan RS, Levy D. Defining diastolic heart failure: a call for standardized diagnostic criteria. Circulation. 2000;101:2118–21.
513. Vasan RS, Benjamin EJ, Levy D. Congestive heart failure with normal left ventricular systolic function. Clinical approaches to the diagnosis and treatment of diastolic heart failure. Arch Intern Med. 1996;156:146–57.
514. Kessler KM. Heart failure with normal systolic function. Update of prevalence, differential diagnosis, prognosis, and therapy. Arch Intern Med. 1988;148:2109–11.
515. Vasan RS, Benjamin EJ, Levy D. Prevalence, clinical features and prognosis of diastolic heart failure: an epidemiologic perspective. J Am Coll Cardiol. 1995;26:1565–74.
516. Nishimura RA, Tajik AJ. Evaluation of diastolic filling of left ventricle in health and disease: doppler echocardiography is the clinician's Rosetta Stone. J Am Coll Cardiol. 1997;30:8–18.
517. Tresch DD. The clinical diagnosis of heart failure in older patients. J Am Geriatr Soc. 1997;45:1128–33.
518. Lenihan DJ, Gerson MC, Hoit BD, et al. Mechanisms, diagnosis, and treatment of diastolic heart failure. Am Heart J. 1995;130:153–66.
519. Ghali JK, Kadakia S, Cooper RS, et al. Bedside diagnosis of preserved versus impaired left ventricular systolic function in heart failure. Am J Cardiol. 1991;67:1002–6.
520. Garcia MJ, Thomas JD, Klein AL. New Doppler echocardiographic applications for the study of diastolic function. J Am Coll Cardiol. 1998;32:865–75.
521. Lubien E, DeMaria A, Krishnaswamy P, et al. Utility of B-natriuretic peptide in detecting diastolic dysfunction: comparison with Doppler velocity recordings. Circulation. 2002;105:595–601.
522. Aronow WS, Kronzon I. Effect of enalapril on congestive heart failure treated with diuretics in elderly patients with prior myocardial infarction and normal left ventricular ejection fraction. Am J Cardiol. 1993;71:602–4.
523. Aronow WS, Ahn C, Kronzon I. Effect of propranolol versus no propranolol on total mortality plus nonfatal myocardial infarction in older patients with prior myocardial infarction, congestive heart failure, and left ventricular ejection fraction > or = 40% treated with diuretics plus angiotensin-converting enzyme inhibitors. Am J Cardiol. 1997;80:207–9.
524. Warner JG Jr., Metzger DC, Kitzman DW, et al. Losartan improves exercise tolerance in patients with diastolic dysfunction and a hypertensive response to exercise. J Am Coll Cardiol. 1999;33:1567–72.
525. Brutsaert DL, Rademakers FE, Sys SU. Triple control of relaxation: implications in cardiac disease. Circulation. 1984;69:190–6.
526. Kjeldsen SE, Dahlof B, Devereux RB, et al. Effects of losartan on cardiovascular morbidity and mortality in patients with isolated systolic hypertension and left ventricular hypertrophy: a Losartan Intervention for Endpoint Reduction (LIFE) substudy. JAMA. 2002;288:1491–8.
527. Cotter G, Weissgarten J, Metzkor E, et al. Increased toxicity of high-dose furosemide versus low-dose dopamine in the treatment of refractory congestive heart failure. Clin Pharmacol Ther. 1997;62:187–93.
528. Faris R, Flather MD, Purcell H, et al. Diuretics for heart failure. Cochrane Database Syst Rev. 2006;CD003838.
529. Costanzo MR, Saltzberg M, O'Sullivan J, et al. Early ultrafiltration in patients with decompensated heart failure and diuretic resistance. J Am Coll Cardiol. 2005;46:2047–51.
530. Domanski M, Norman J, Pitt B, et al. Diuretic use, progressive heart failure, and death in patients in the Studies Of Left Ventricular Dysfunction (SOLVD). J Am Coll Cardiol. 2003;42:705–8.
531. Cicoira M, Zanolla L, Rossi A, et al. Long-term, dose-dependent effects of spironolactone on left ventricular function and exercise tolerance in patients with chronic heart failure. J Am Coll Cardiol. 2002;40:304–10.
532. Faris R, Flather M, Purcell H, et al. Current evidence supporting the role of diuretics in heart failure: a meta analysis of randomised controlled trials. Int J Cardiol. 2002;82:149–58.
533. Jessup M, Banner N, Brozena S, et al. Optimal pharmacologic and non-pharmacologic management of cardiac transplant candidates: approaches to be considered prior to transplant evaluation: International Society for Heart and Lung Transplantation guidelines for the care of cardiac transplant candidates—2006. J Heart Lung Transplant. 2006;25:1003–23.
534. McAlister FA, Lawson FM, Teo KK, et al. A systematic review of randomized trials of disease management programs in heart failure. Am J Med. 2001;110:378–84.
535. Whellan DJ, Hasselblad V, Peterson E, et al. Metaanalysis and review of heart failure disease management randomized controlled clinical trials. Am Heart J. 2005;149:722–9.
536. Yancy CW, Krum H, Massie BM, et al. The Second Follow-up Serial Infusions of Nesiritide (FUSION II) trial for advanced heart failure: study rationale and design. Am Heart J. 2007;153:478–84.
537. Clark RA, Inglis SC, McAlister FA, et al. Telemonitoring or structured telephone support programmes for patients with chronic heart failure: systematic review and meta-analysis. BMJ. 2007;334:942.
538. Rose EA, Gelijns AC, Moskowitz AJ, et al. Long-term mechanical left ventricular assistance for end-stage heart failure. N Engl J Med. 2001;345:1435–43.
539. Lietz K, Long JW, Kfoury AG, et al. Outcomes of left ventricular assist device implantation as destination therapy in the post-REMATCH era: implications for patient selection. Circulation. 2007;116:497–505.
540. Connors AF Jr., Speroff T, Dawson NV, et al., for the SUPPORT Investigators. The effectiveness of right heart catheterization in the initial care of critically ill patients. JAMA. 1996;276:889–97.
541. Wu AH, Aaronson KD, Bolling SF, et al. Impact of mitral valve annuloplasty on mortality risk in patients with mitral regurgitation and left ventricular systolic dysfunction. J Am Coll Cardiol. 2005;45:381–7.
542. Mann DL, Acker MA, Jessup M, et al. Clinical evaluation of the CorCap Cardiac Support Device in patients with dilated cardiomyopathy. Ann Thorac Surg. 2007;84:1226–35.
543. Sindone AP, Keogh AM, Macdonald PS, et al. Continuous home ambulatory intravenous inotropic drug therapy in severe heart failure: safety and cost efficacy. Am Heart J. 1997;134:889–900.
544. Miller LW, Merkle EJ, Herrmann V. Outpatient dobutamine for end-stage congestive heart failure. Crit Care Med. 1990;18:S30–S33.
545. Krell MJ, Kline EM, Bates ER, et al. Intermittent, ambulatory dobutamine infusions in patients with severe congestive heart failure. Am Heart J. 1986;112:787–91.
546. Oliva F, Latini R, Politi A, et al. Intermittent 6-month low-dose dobutamine infusion in severe heart failure: DICE multicenter trial. Am Heart J. 1999;138:247–53.
547. Pepi M, Marenzi GC, Agostoni PG, et al. Sustained cardiac diastolic changes elicited by ultrafiltration in patients with moderate congestive heart failure: pathophysiological correlates. Br Heart J. 1993;70:135–40.
548. Iorio L, Simonelli R, Nacca RG, et al. Daily hemofiltration in severe heart failure. Kidney Int Suppl. 1997;59:S62–5.
549. Ashton CM, Kuykendall DH, Johnson ML, et al. The association between the quality of inpatient care and early readmission. Ann Intern Med. 1995;122:415–21.
550. Ljungman S, Kjekshus J, Swedberg K. Renal function in severe congestive heart failure during treatment with enalapril (the Cooperative North Scandinavian Enalapril Survival Study [CONSENSUS] Trial). Am J Cardiol. 1992;70:479–87.
551. Bristow MR, Gilbert EM, Abraham WT, et al., for the MOCHA Investigators. Carvedilol produces dose-related improvements in left ventricular function and survival in subjects with chronic heart failure. Circulation. 1996;94:2807–16.

552. Pitt B, Segal R, Martinez FA, et al. Randomised trial of losartan versus captopril in patients over 65 with heart failure (Evaluation of Losartan in the Elderly Study, ELITE). Lancet. 1997;349:747–52.
553. Massie BM, Kramer BL, Topic N. Lack of relationship between the short-term hemodynamic effects of captopril and subsequent clinical responses. Circulation. 1984;69:1135–41.
554. Stevenson LW, Massie BM, Francis GS. Optimizing therapy for complex or refractory heart failure: a management algorithm. Am Heart J. 1998;135:S293–S309.
555. Mudge GH, Goldstein S, Addonizio LJ, et al. 24th Bethesda conference: cardiac transplantation. Task Force 3: recipient guidelines/prioritization. J Am Coll Cardiol. 1993;22:21–31.
556. Miller LW. Listing criteria for cardiac transplantation: results of an American Society of Transplant Physicians-National Institutes of Health conference. Transplantation. 1998;66:947–51.
557. Mancini DM, Eisen H, Kussmaul W, et al. Value of peak exercise oxygen consumption for optimal timing of cardiac transplantation in ambulatory patients with heart failure. Circulation. 1991;83:778–86.
558. Magovern GJ. Introduction to the history and development of skeletal muscle plasticity and its clinical application to cardiomyoplasty and skeletal muscle ventricle. Semin Thorac Cardiovasc Surg. 1991;3:95–7.
559. Batista RJ, Verde J, Nery P, et al. Partial left ventriculectomy to treat end-stage heart disease. Ann Thorac Surg. 1997;64:634–8.
560. McCarthy JF, McCarthy PM, Starling RC, et al. Partial left ventriculectomy and mitral valve repair for end-stage congestive heart failure. Eur J Cardiothorac Surg. 1998;13:337–43.
561. Goldstein DJ, Oz MC, Rose EA. Implantable left ventricular assist devices. N Engl J Med. 1998;339:1522–33.
562. Rose EA, Moskowitz AJ, Packer M, et al. The REMATCH trial: rationale, design, and end points. Randomized Evaluation of Mechanical Assistance for the Treatment of Congestive Heart Failure. Ann Thorac Surg. 1999;67:723–30.
563. Helman DN, Maybaum SW, Morales DL, et al. Recurrent remodeling after ventricular assistance: is long-term myocardial recovery attainable? Ann Thorac Surg. 2000;70:1255–8.
564. Chin MH, Goldman L. Gender differences in 1-year survival and quality of life among patients admitted with congestive heart failure. Med Care. 1998;36:1033–46.
565. Maisel AS, Krishnaswamy P, Nowak RM, et al. Rapid measurement of B-type natriuretic peptide in the emergency diagnosis of heart failure. N Engl J Med. 2002;347:161–7.
566. Moe GW, Howlett J, Januzzi JL, et al. N-terminal pro-B-type natriuretic peptide testing improves the management of patients with suspected acute heart failure: primary results of the Canadian prospective randomized multicenter IMPROVE-CHF study. Circulation. 2007;115:3103–10.
567. Mebazaa A, Gheorghiade M, Pina IL, et al. Practical recommendations for prehospital and early in-hospital management of patients presenting with acute heart failure syndromes. Crit Care Med. 2008;36:S129–S139.
568. Costanzo MR, Johannes RS, Pine M, et al. The safety of intravenous diuretics alone versus diuretics plus parenteral vasoactive therapies in hospitalized patients with acutely decompensated heart failure: a propensity score and instrumental variable analysis using the Acutely Decompensated Heart Failure National Registry (ADHERE) database. Am Heart J. 2007;154:267–77.
569. Metra M, Torp-Pedersen C, Cleland JG, et al. Should beta-blocker therapy be reduced or withdrawn after an episode of decompensated heart failure? Results from COMET. Eur J Heart Fail. 2007;9:901–9.
570. Fonarow GC, Abraham WT, Albert NM, et al. Influence of beta-blocker continuation or withdrawal on outcomes in patients hospitalized with heart failure: findings from the OPTIMIZE-HF program. J Am Coll Cardiol. 2008;52:190–9.
571. Lappe JM, Muhlestein JB, Lappe DL, et al. Improvements in 1-year cardiovascular clinical outcomes associated with a hospital-based discharge medication program. Ann Intern Med. 2004;141:446–53.
572. Naylor M, Brooten D, Jones R, et al. Comprehensive discharge planning for the hospitalized elderly. A randomized clinical trial. Ann Intern Med. 1994;120:999–1006.
573. Naylor MD, Brooten DA, Campbell RL, et al. Transitional care of older adults hospitalized with heart failure: a randomized, controlled trial. J Am Geriatr Soc. 2004;52:675–84.
574. Casey DE Jr., Abraham WT, Guo L, et al. Reducing heart failure hospitalizations and readmissions with Heart Failure Advocates: a call to action for nursing. Circulation. 2007;115:e559–60.
575. Windham BG, Bennett RG, Gottlieb S. Care management interventions for older patients with congestive heart failure. Am J Manag Care. 2003;9:447–59.
576. Phillips CO, Wright SM, Kern DE, et al. Comprehensive discharge planning with postdischarge support for older patients with congestive heart failure: a meta-analysis. JAMA. 2004;291:1358–67.
577. Koelling TM, Johnson ML, Cody RJ, et al. Discharge education improves clinical outcomes in patients with chronic heart failure. Circulation. 2005;111:179–85.
578. Costanzo MR, Guglin ME, Saltzberg MT, et al. Ultrafiltration versus intravenous diuretics for patients hospitalized for acute decompensated heart failure. J Am Coll Cardiol. 2007;49:675–83.
579. Cuffe MS, Califf RM, Adams KF Jr., et al. Short-term intravenous milrinone for acute exacerbation of chronic heart failure: a randomized controlled trial. JAMA. 2002;287:1541–7.
580. Binanay C, Califf RM, Hasselblad V, et al. Evaluation study of congestive heart failure and pulmonary artery catheterization effectiveness: the ESCAPE trial. JAMA. 2005;294:1625–33.
581. Bhatia RS, Tu JV, Lee DS, et al. Outcome of heart failure with preserved ejection fraction in a population-based study. N Engl J Med. 2006;355:260–9.
582. Solomon SD, Dobson J, Pocock S, et al. Influence of nonfatal hospitalization for heart failure on subsequent mortality in patients with chronic heart failure. Circulation. 2007;116:1482–7.
583. Fonarow GC, Heywood JT, Heidenreich PA, et al. Temporal trends in clinical characteristics, treatments, and outcomes for heart failure hospitalizations, 2002 to 2004: findings from Acute Decompensated Heart Failure National Registry (ADHERE). Am Heart J. 2007;153:1021–8.
584. Brown DW, Haldeman GA, Croft JB, et al. Racial or ethnic differences in hospitalization for heart failure among elderly adults: Medicare, 1990 to 2000. Am Heart J. 2005;150:448–54.
585. Klapholz M, Maurer M, Lowe AM, et al. Hospitalization for heart failure in the presence of a normal left ventricular ejection fraction: results of the New York Heart Failure Registry. J Am Coll Cardiol. 2004;43:1432–8.
586. Haldeman GA, Croft JB, Giles WH, et al. Hospitalization of patients with heart failure: National Hospital Discharge Survey, 1985 to 1995. Am Heart J. 1999;137:352–60.
587. Konstam MA, Gheorghiade M, Burnett JC Jr., et al. Effects of oral tolvaptan in patients hospitalized for worsening heart failure: the EVEREST Outcome Trial. JAMA. 2007;297:1319–31.
588. Young JB, Abraham WT, Bourge RC, et al. Task force 8: training in heart failure endorsed by the Heart Failure Society of America. J Am Coll Cardiol. 2008;51:383–9.
589. Adams J, Lindenfeld J, Arnold J, et al. HFSA 2006 Comprehensive Heart Failure Practice Guideline. J Card Fail. 2006;12:e1–119.
589a. Dickstein K, Cohen-Solal A, Filippatos G, et al. ESC guidelines for the diagnosis and treatment of acute and chronic heart failure 2008. Eur Heart J. 2008;29:2388–442.
590. Cotter G, Felker GM, Adams KF, et al. The pathophysiology of acute heart failure—is it all about fluid accumulation? Am Heart J. 2008;155:9–18.
591. Cleland JG, Swedberg K, Follath F, et al. The EuroHeart Failure survey programme—a survey on the quality of care among patients with heart failure in Europe. Part 1: patient characteristics and diagnosis. Eur Heart J. 2003;24:442–63.
592. Latini R, Masson S, Anand IS, et al. Prognostic value of very low plasma concentrations of troponin T in patients with stable chronic heart failure. Circulation. 2007;116:1242–9.
593. Anderson JL, Adams CD, Antman EM, et al. ACC/AHA 2007 guidelines for the management of patients with unstable angina/non–ST-elevation myocardial infarction: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (Writing Committee to Revise the 2002 Guidelines for the Management of Patients With Unstable Angina/Non-ST-Elevation Myocardial Infarction) developed in collaboration with the American College of Emergency Physicians, the Society for Cardiovascular Angiography and Interventions, and the Society of Thoracic Surgeons endorsed by the American Association of Cardiovascular

and Pulmonary Rehabilitation and the Society for Academic Emergency Medicine. J Am Coll Cardiol. 2007;50:e1–157.
594. Peacock WF, Fonarow GC, Emerman CL, et al. Impact of early initiation of intravenous therapy for acute decompensated heart failure on outcomes in ADHERE. Cardiology. 2007;107:44–51.
595. Maisel AS, Peacock WF, McMullin N, et al. Timing of immunoreactive B-type natriuretic peptide levels and treatment delay in acute decompensated heart failure: an ADHERE (Acute Decompensated Heart Failure National Registry) analysis. J Am Coll Cardiol. 2008;52:534–40.
596. Shankar SS, Brater DC. Loop diuretics: from the Na-K-2Cl transporter to clinical use. Am J Physiol Renal Physiol. 2003;284:F11–21.
597. Wilcox CS, Mitch WE, Kelly RA, et al. Response of the kidney to furosemide. I. Effects of salt intake and renal compensation. J Lab Clin Med. 1983;102:450–8.
598. Cleland JG, Coletta A, Witte K. Practical applications of intravenous diuretic therapy in decompensated heart failure. Am J Med. 2006; 119:S26–S36.
599. Firth JD, Raine AE, Ledingham JG. Raised venous pressure: a direct cause of renal sodium retention in oedema? Lancet. 1988;1:1033–5.
600. Pivac N, Rumboldt Z, Sardelic S, et al. Diuretic effects of furosemide infusion versus bolus injection in congestive heart failure. Int J Clin Pharmacol Res. 1998;18:121–8.
601. Salvador DR, Rey NR, Ramos GC, et al. Continuous infusion versus bolus injection of loop diuretics in congestive heart failure. Cochrane Database Syst Rev. 2005;CD003178.
602. Bourge RC, Tallaj JA. Ultrafiltration: a new approach toward mechanical diuresis in heart failure. J Am Coll Cardiol. 2005;46: 2052–3.
603. Bart BA, Boyle A, Bank AJ, et al. Ultrafiltration versus usual care for hospitalized patients with heart failure: the Relief for Acutely Fluid-Overloaded Patients With Decompensated Congestive Heart Failure (RAPID-CHF) trial. J Am Coll Cardiol. 2005;46:2043–6.
604. Jaski BE, Ha J, Denys BG, et al. Peripherally inserted veno-venous ultrafiltration for rapid treatment of volume overloaded patients. J Card Fail. 2003;9:227–31.
605. Dupuis J, Lalonde G, Lemieux R, et al. Tolerance to intravenous nitroglycerin in patients with congestive heart failure: role of increased intravascular volume, neurohumoral activation and lack of prevention with N-acetylcysteine. J Am Coll Cardiol. 1990;16:923–31.
606. Fung HL, Bauer JA. Mechanisms of nitrate tolerance. Cardiovasc Drugs Ther. 1994;8:489–99.
607. Elkayam U, Kulick D, McIntosh N, et al. Incidence of early tolerance to hemodynamic effects of continuous infusion of nitroglycerin in patients with coronary artery disease and heart failure. Circulation. 1987;76:577–84.
608. Wang DJ, Dowling TC, Meadows D, et al. Nesiritide does not improve renal function in patients with chronic heart failure and worsening serum creatinine. Circulation. 2004;110:1620–5.
609. Witteles RM, Kao D, Christopherson D, et al. Impact of nesiritide on renal function in patients with acute decompensated heart failure and pre-existing renal dysfunction a randomized, double-blind, placebo-controlled clinical trial. J Am Coll Cardiol. 2007;50:1835–40.
610. Silver MA, Yancy CW. Using homeostatic peptides in decompensated heart failure a reasonable paradigm but a flawed practice? J Am Coll Cardiol. 2007;50:1841–3.
611. O'Connor CM, Gattis WA, Uretsky BF, et al. Continuous intravenous dobutamine is associated with an increased risk of death in patients with advanced heart failure: insights from the Flolan International Randomized Survival Trial (FIRST). Am Heart J. 1999;138:78–86.
612. Elkayam U, Tasissa G, Binanay C, et al. Use and impact of inotropes and vasodilator therapy in hospitalized patients with severe heart failure. Am Heart J. 2007;153:98–104.
613. Abraham WT, Adams KF, Fonarow GC, et al. In-hospital mortality in patients with acute decompensated heart failure requiring intravenous vasoactive medications: an analysis from the Acute Decompensated Heart Failure National Registry (ADHERE). J Am Coll Cardiol. 2005;46:57–64.
614. Shah MR, Hasselblad V, Stevenson LW, et al. Impact of the pulmonary artery catheter in critically ill patients: meta-analysis of randomized clinical trials. JAMA. 2005;294:1664–70.
615. Geerts WH, Pineo GF, Heit JA, et al. Prevention of venous thromboembolism: the Seventh ACCP Conference on Antithrombotic and Thrombolytic Therapy. Chest. 2004;126:338S–400S.
616. Bonow RO, Bennett S, Casey DE Jr., et al. ACC/AHA clinical performance measures for adults with chronic heart failure: a report of the American College of Cardiology/American Heart Association Task Force on Performance Measures (Writing Committee to Develop Heart Failure Clinical Performance Measures) endorsed by the Heart Failure Society of America. J Am Coll Cardiol. 2005;46:1144–78.
617. Fonarow GC, Yancy CW, Heywood JT. Adherence to heart failure quality-of-care indicators in US hospitals: analysis of the ADHERE Registry. Arch Intern Med. 2005;165:1469–77.
618. Krumholz HM, Baker DW, Ashton CM, et al. Evaluating quality of care for patients with heart failure. Circulation. 2000;101:e122–40.
619. Gislason GH, Rasmussen JN, Abildstrom SZ, et al. Persistent use of evidence-based pharmacotherapy in heart failure is associated with improved outcomes. Circulation. 2007;116:737–44.
620. The Agency for Healthcare Quality and Research 30 Safe Practices for Better Health Care. Available at: http://www.ahrq.gov/qual/30safe.htm. Accessed March 1, 2008.
621. The Joint Commission2008 National Patient Saftey Goals. Available at: http://www.jointcommission.org/PatientSafety/NationalPatientSafetyGoals/08_hap_npsgs.htm. Accessed March 1, 2008.
622. Levenson JW, McCarthy EP, Lynn J, et al. The last six months of life for patients with congestive heart failure. J Am Geriatr Soc. 2000; 48:S101–9.
623. Morrison RS, Maroney-Galin C, Kralovec PD, et al. The growth of palliative care programs in United States hospitals. J Palliat Med. 2005;8:1127–34.
624. Qaseem A, Snow V, Shekelle P, et al. Evidence-based interventions to improve the palliative care of pain, dyspnea, and depression at the end of life: a clinical practice guideline from the American College of Physicians. Ann Intern Med. 2008;148:141–6.
625. Lorenz KA, Lynn J, Dy SM, et al. Evidence for improving palliative care at the end of life: a systematic review. Ann Intern Med. 2008;148:147–59.
625a. Lorenz K, Lynn J, Dy S, et al. Evidence for improving palliative care at the end of life: a systematic review. Ann Intern Med. 2008;148:147–59.
625b. Qaseem A, Snow V, Shekelle P, et al. Evidence-based interventions to improve the palliative care of pain, dyspnea, and depression at the end of life: a clinical practice guideline from the American College of Physicians. Ann Intern Med. 2008;148:141–6.
626. Trivedi AN, Zaslavsky AM, Schneider EC, et al. Relationship between quality of care and racial disparities in Medicare health plans. JAMA. 2006;296:1998–2004.
627. Yancy CW. The prevention of heart failure in minority communities and discrepancies in health care delivery systems. Med Clin North Am. 2004;88:1347–68.
628. Clinical Quality Improvement Network Investigators. Mortality risk and patterns of practice in 4606 acute care patients with congestive heart failure. The relative importance of age, sex, and medical therapy. Arch Intern Med. 1996;156:1669–73.
629. Herholz H, Goff DC, Ramsey DJ, et al. Women and Mexican Americans receive fewer cardiovascular drugs following myocardial infarction than men and non-Hispanic whites: the Corpus Christi Heart Project, 1988–1990. J Clin Epidemiol. 1996;49:279–87.
630. Stafford RS, Saglam D, Blumenthal D. National patterns of angiotensin-converting enzyme inhibitor use in congestive heart failure. Arch Intern Med. 1997;157:2460–4.
631. Kimmelstiel C, Goldberg RJ. Congestive heart failure in women: focus on heart failure due to coronary artery disease and diabetes. Cardiology. 1990;77 Suppl 2:71–9:71–9.
632. Shekelle PG, Rich MW, Morton SC, et al. Efficacy of angiotensin-converting enzyme inhibitors and beta-blockers in the management of left ventricular systolic dysfunction according to race, gender, and diabetic status: a meta-analysis of major clinical trials. J Am Coll Cardiol. 2003;41:1529–38.
633. Kostis JB, Shelton B, Gosselin G, et al., for the SOLVD Investigators. Adverse effects of enalapril in the Studies of Left Ventricular Dysfunction (SOLVD). Am Heart J. 1996;131:350–5.
634. Cheitlin MD, Hutter AM Jr., Brindis RG, et al. ACC/AHA expert consensus document. Use of sildenafil (Viagra) in patients with cardiovascular disease. American College of Cardiology/American Heart Association. J Am Coll Cardiol. 1999;33:273–82.
635. Webb DJ, Muirhead GJ, Wulff M, et al. Sildenafil citrate potentiates the hypotensive effects of nitric oxide donor drugs in male patients with stable angina. J Am Coll Cardiol. 2000;36:25–31.

636. Witzig R. The medicalization of race: scientific legitimization of a flawed social construct. Ann Intern Med. 1996;125:675–9.
637. Dries DL, Exner DV, Gersh BJ, et al. Racial differences in the outcome of left ventricular dysfunction [published erratum appears in N Engl J Med 1999;341:298]. N Engl J Med. 1999;340:609–16.
638. Alexander M, Grumbach K, Remy L, et al. Congestive heart failure hospitalizations and survival in California: patterns according to race/ethnicity. Am Heart J. 1999;137:919–27.
639. Philbin EF, DiSalvo TG. Influence of race and gender on care process, resource use, and hospital-based outcomes in congestive heart failure. Am J Cardiol. 1998;82:76–81.
640. Rathore SS, Foody JM, Wang Y, et al. Race, quality of care, and outcomes of elderly patients hospitalized with heart failure. JAMA. 2003;289:2517–24.
641. Ayanian JZ, Weissman JS, Chasan-Taber S, et al. Quality of care by race and gender for congestive heart failure and pneumonia. Med Care. 1999;37:1260–9.
642. Committee on Understanding and Eliminating Racial and Ethnic Disparities in Health Care. Smedley BD, Stith AY, Nelson AR, editors. Unequal Treatment: Confronting Racial and Ethnic Disparities in Health Care. Washington, DC: National Academy Press, 2003.
643. Oster A, Bindman AB. Emergency department visits for ambulatory care sensitive conditions: insights into preventable hospitalizations. Med Care. 2003;41:198–207.
644. Davis SK, Liu Y, Gibbons GH. Disparities in trends of hospitalization for potentially preventable chronic conditions among African Americans during the 1990s: implications and benchmarks. Am J Public Health. 2003;93:447–55.
645. Exner DV, Dries DL, Domanski MJ, et al. Lesser response to angiotensin-converting-enzyme inhibitor therapy in black as compared with white patients with left ventricular dysfunction. N Engl J Med. 2001;344:1351–7.
646. Domanski MJ, Borkowf CB, Campeau L, et al., for the Post-CABG Trial Investigators. Prognostic factors for atherosclerosis progression in saphenous vein grafts: the postcoronary artery bypass graft (Post-CABG) trial. J Am Coll Cardiol. 2000;36:1877–83.
647. Yancy CW, Fowler MB, Colucci WS, et al. Race and the response to adrenergic blockade with carvedilol in patients with chronic heart failure. N Engl J Med. 2001;344:1358–65.
648. Jarcho J, Naftel DC, Shroyer TW, et al., for the Cardiac Transplant Research Database Group. Influence of HLA mismatch on rejection after heart transplantation: a multiinstitutional study. J Heart Lung Transplant. 1994;13:583–95.
649. Suthanthiran M, Li B, Song JO, et al. Transforming growth factor-beta 1 hyperexpression in African-American hypertensives: A novel mediator of hypertension and/or target organ damage. Proc Natl Acad Sci U S A. 2000;97:3479–84.
650. McNamara DM, Holubkov R, Janosko K, et al. Pharmacogenetic interactions between beta-blocker therapy and the angiotensin-converting enzyme deletion polymorphism in patients with congestive heart failure. Circulation. 2001;103:1644–8.
651. Mason DA, Moore JD, Green SA, et al. A gain-of-function polymorphism in a G-protein coupling domain of the human beta1-adrenergic receptor. J Biol Chem. 1999;274:12670–4.
652. Small KM, Wagoner LE, Levin AM, et al. Synergistic polymorphisms of beta1- and alpha2C-adrenergic receptors and the risk of congestive heart failure. N Engl J Med. 2002;347:1135–42.
653. Kupari M, Lindroos M, Iivanainen AM, et al. Congestive heart failure in old age: prevalence, mechanisms and 4–year prognosis in the Helsinki Ageing Study. J Intern Med. 1997;241:387–94.
654. Wolinsky FD, Overhage JM, Stump TE, et al. The risk of hospitalization for congestive heart failure among older adults. Med Care. 1997;35:1031–43.
655. Philbin EF, Rocco TA Jr., Lynch LJ, et al. Predictors and determinants of hospital length of stay in congestive heart failure in ten community hospitals. J Heart Lung Transplant. 1997;16:548–55.
656. Candlish P, Watts P, Redman S, et al. Elderly patients with heart failure: a study of satisfaction with care and quality of life. Int J Qual Health Care. 1998;10:141–6.
657. Krumholz HM, Parent EM, Tu N, et al. Readmission after hospitalization for congestive heart failure among Medicare beneficiaries. Arch Intern Med. 1997;157:99–104.
658. Zieman SJ, Fortuin NJ. Hypertrophic and restrictive cardiomyopathies in the elderly. Cardiol Clin. 1999;17:159–72.
659. Hughes CV, Wong M, Johnson G, et al., for the V-HeFT VA Cooperative Studies Group. Influence of age on mechanisms and prognosis of heart failure. Circulation. 1993;87:VI111–7.
660. Kober L, Torp-Pedersen C, Ottesen M, et al., for the TRACE Study Group. Influence of gender on short- and long-term mortality after acute myocardial infarction. Am J Cardiol. 1996;77:1052–6.
661. Cody RJ, Torre S, Clark M, et al. Age-related hemodynamic, renal, and hormonal differences among patients with congestive heart failure. Arch Intern Med. 1989;149:1023–8.
662. Doba N, Tomiyama H, Nakayama T. Drugs, heart failure and quality of life: what are we achieving? What should we be trying to achieve? Drugs Aging. 1999;14:153–63.
663. ACE Inhibitor Myocardial Infarction Collaborative Group. Indications for ACE inhibitors in the early treatment of acute myocardial infarction: systematic overview of individual data from 100,000 patients in randomized trials. Circulation. 1998;97:2202–12.
664. Murray MD, Haag KM, Black PK, et al. Variable furosemide absorption and poor predictability of response in elderly patients. Pharmacotherapy. 1997;17:98–106.
665. Robinson T, Gariballa S, Fancourt G, et al. The acute effects of a single dopamine infusion in elderly patients with congestive cardiac failure. Br J Clin Pharmacol. 1994;37:261–3.
666. Aronow WS. Postinfarction use of beta-blockers in elderly patients. Drugs Aging. 1997;11:424–32.
667. Schwartz JB. Calcium antagonists in the elderly. A risk-benefit analysis. Drugs Aging. 1996;9:24–36.
668. Wenger AL. Oral anticoagulant therapy at elderly age: heart failure and nonvalvular atrial fibrillation. Am J Ger Card. 1996;5:78–83.
669. Rich MW, Woods WL, Davila-Roman VG, et al. A randomized comparison of intravenous amrinone versus dobutamine in older patients with decompensated congestive heart failure. J Am Geriatr Soc. 1995;43:271–4.
670. Morisco C, Condorelli M, Crepaldi G, et al. Lisinopril in the treatment of congestive heart failure in elderly patients: comparison versus captopril. Cardiovasc Drugs Ther. 1997;11:63–9.
671. Rich MW, Gray DB, Beckham V, et al. Effect of a multidisciplinary intervention on medication compliance in elderly patients with congestive heart failure. Am J Med. 1996;101:270–6.
672. Ni H, Nauman DJ, Hershberger RE. Managed care and outcomes of hospitalization among elderly patients with congestive heart failure. Arch Intern Med. 1998;158:1231–6.
673. Ware JE Jr., Bayliss MS, Rogers WH, et al. Differences in 4-year health outcomes for elderly and poor, chronically ill patients treated in HMO and fee-for-service systems. Results from the Medical Outcomes Study. JAMA. 1996;276:1039–47.
674. Solang L, Malmberg K, Ryden L. Diabetes mellitus and congestive heart failure. Further knowledge needed. Eur Heart J. 1999;20:789–95.
675. Vasan RS, Larson MG, Benjamin EJ, et al. Congestive heart failure in subjects with normal versus reduced left ventricular ejection fraction: prevalence and mortality in a population-based cohort. J Am Coll Cardiol. 1999;33:1948–55.
676. Sahai A, Ganguly PK. Congestive heart failure in diabetes with hypertension may be due to uncoupling of the atrial natriuretic peptide receptor-effector system in the kidney basolateral membrane. Am Heart J. 1991;122:164–70.
677. Galderisi M, Anderson KM, Wilson PW, et al. Echocardiographic evidence for the existence of a distinct diabetic cardiomyopathy (the Framingham Heart Study). Am J Cardiol. 1991;68:85–9.
678. Zarich SW, Nesto RW. Diabetic cardiomyopathy. Am Heart J. 1989;118:1000–12.
679. Randomised trial of cholesterol lowering in 4444 patients with coronary heart disease: the Scandinavian Simvastatin Survival Study (4S). Lancet. 1994;344:1383–9.
680. SHEP Cooperative Research Group. Prevention of stroke by antihypertensive drug treatment in older persons with isolated systolic hypertension. Final results of the Systolic Hypertension in the Elderly Program (SHEP). JAMA. 1991;265:3255–64.
681. Curb JD, Pressel SL, Cutler JA, et al., for the Systolic Hypertension in the Elderly Program Cooperative Research Group. Effect of diuretic-based antihypertensive treatment on cardiovascular disease risk in older diabetic patients with isolated systolic hypertension. [published erratum appears in JAMA 1997;277:1356]. JAMA. 1996;276:1886–92.

682. Swan JW, Anker SD, Walton C, et al. Insulin resistance in chronic heart failure: relation to severity and etiology of heart failure. J Am Coll Cardiol. 1997;30:527–32.
683. Watanabe K, Sekiya M, Tsuruoka T, et al. Relationship between insulin resistance and cardiac sympathetic nervous function in essential hypertension. J Hypertens. 1999;17:1161–8.
684. Zimlichman R, Zaidel L, Nofech-Mozes S, et al. Hyperinsulinemia induces myocardial infarctions and arteriolar medial hypertrophy in spontaneously hypertensive rats. Am J Hypertens. 1997;10:646–53.
685. Holmang A, Yoshida N, Jennische E, et al. The effects of hyperinsulinaemia on myocardial mass, blood pressure regulation and central haemodynamics in rats. Eur J Clin Invest. 1996;26:973–8.
686. Zimlichman R, Zeidel L, Gefel D, et al. Insulin induces medial hypertrophy of myocardial arterioles in rats. Am J Hypertens. 1995;8:915–20.
687. Krentz AJ, Bailey CJ, Melander A. Thiazolidinediones for type 2 diabetes. New agents reduce insulin resistance but need long term clinical trials. BMJ. 2000;321:252–3.
688. Nesto RW, Bell D, Bonow RO, et al. Thiazolidinedione use, fluid retention, and congestive heart failure: a consensus statement from the American Heart Association and American Diabetes Association. October 7, 2003. Circulation. 2003;108:2941–8.
689. Schulman DS, Flores AR, Tugoen J, et al. Antihypertensive treatment in hypertensive patients with normal left ventricular mass is associated with left ventricular remodeling and improved diastolic function. Am J Cardiol. 1996;78:56–60.
690. Habib GB, Mann DL, Zoghbi WA. Normalization of cardiac structure and function after regression of cardiac hypertrophy. Am Heart J. 1994;128:333–43.
691. Ryden L, Armstrong P, Cleland JG, for the ATLAS Investigators. High dose ACE-inhibitor strategy is more effectice than low-dose in diabetic patients with congestive heart failure (abstr). J Am Coll Cardiol. 1999;33 Suppl A:188.
692. Packer M, Kukin ML. Management of patients with heart failure and angina: do coexistent diseases alter the response to cardiovascular drugs? [editorial comment]. J Am Coll Cardiol. 1991;17:740–2.
693. Elkayam U, Johnson JV, Shotan A, et al. Intermittent large dose nitrates added to standard therapy, improves left ventricular function and exercise capacity in patients with chronic heart failure (abstr). J Am Coll Cardiol. 1999;33 Suppl A:188.
694. Sussex BA, Campbell NR, Raju MK, et al. The antianginal efficacy of isosorbide dinitrate therapy is maintained during diuretic treatment. Clin Pharmacol Ther. 1994;56:229–34.
695. Parker JD, Parker AB, Farrell B, et al. Effects of diuretic therapy on the development of tolerance to nitroglycerin and exercise capacity in patients with chronic stable angina. Circulation. 1996;93:691–6.
696. Agostoni PG, De Cesare N, Doria E, et al. Afterload reduction: a comparison of captopril and nifedipine in dilated cardiomyopathy. Br Heart J. 1986;55:391–9.
697. Tan LB, Murray RG, Littler WA. Felodipine in patients with chronic heart failure: discrepant haemodynamic and clinical effects. Br Heart J. 1987;58:122–8.
698. Elkayam U, Amin J, Mehra A, et al. A prospective, randomized, double-blind, crossover study to compare the efficacy and safety of chronic nifedipine therapy with that of isosorbide dinitrate and their combination in the treatment of chronic congestive heart failure. Circulation. 1990;82:1954–61.
699. Cohn JN, Ziesche S, Smith R, et al., for the Vasodilator-Heart Failure Trial (V-HeFT) Study Group. Effect of the calcium antagonist felodipine as supplementary vasodilator therapy in patients with chronic heart failure treated with enalapril: V-HeFT III. Circulation. 1997;96:856–63.
700. Packer M. Calcium channel blockers in chronic heart failure. The risks of "physiologically rational" therapy [editorial; comment]. Circulation. 1990;82:2254–7.
701. Elkayam U, Weber L, McKay C, et al. Spectrum of acute hemodynamic effects of nifedipine in severe congestive heart failure. Am J Cardiol. 1985;56:560–6.
702. Barjon JN, Rouleau JL, Bichet D, et al. Chronic renal and neurohumoral effects of the calcium entry blocker nisoldipine in patients with congestive heart failure. J Am Coll Cardiol. 1987;9:622–30.
703. Goldstein RE, Boccuzzi SJ, Cruess D, et al., for the Adverse Experience Committee and the Multicenter Diltiazem Postinfarction Research Group. Diltiazem increases late-onset congestive heart failure in postinfarction patients with early reduction in ejection fraction. Circulation. 1991;83:52–60.
704. Littler WA, Sheridan DJ., for the UK Study Group. Placebo controlled trial of felodipine in patients with mild to moderate heart failure. Br Heart J. 1995;73:428–33.
705. Mohindra SK, Udeani GO. Long-acting verapamil and heart failure [letter]. JAMA. 1989;261:994.
706. Mullins ME, Horowitz BZ, Linden DH, et al. Life-threatening interaction of mibefradil and beta-blockers with dihydropyridine calcium channel blockers. JAMA. 1998;280:157–8.
707. Benatar D, Hall V, Reddy S, et al. Clinical and neurohormonal effects of nicardipine hydrochloride in patients with severe chronic heart failure receiving angiotensin-converting enzyme inhibitor therapy. Am J Ther. 1998;5:25–32.
708. Levine TB, Bernink PJ, Caspi A, et al. Effect of mibefradil, a T-type calcium channel blocker, on morbidity and mortality in moderate to severe congestive heart failure: the MACH-1 study. Mortality Assessment in Congestive Heart Failure Trial. Circulation. 2000; 101:758–64.
709. Quality of life in patients randomly assigned to treatment groups. Coronary artery surgery study (CASS): a randomized trial of coronary artery bypass surgery. Circulation. 1983;68:951–60.
710. Parisi AF, Folland ED, Hartigan P, for the Veterans Affairs ACME Investigators. A comparison of angioplasty with medical therapy in the treatment of single-vessel coronary artery disease. N Engl J Med. 1992;326:10–6.
711. Passamani E, Davis KB, Gillespie MJ, et al. A randomized trial of coronary artery bypass surgery. Survival of patients with a low ejection fraction. N Engl J Med. 1985;312:1665–71.
712. Gibbons RJ, Chatterjee K, Daley J, et al. ACC/AHA/ACP-ASIM guidelines for the management of patients with chronic stable angina: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (Committee on Management of Patients With Chronic Stable Angina). J Am Coll Cardiol. 1999;33:2092–197.
713. Yusuf S, Pepine CJ, Garces C, et al. Effect of enalapril on myocardial infarction and unstable angina in patients with low ejection fractions. Lancet. 1992;340:1173–8.
714. Rutherford JD, Pfeffer MA, Moye LA, et al., for the SAVE Investigators. Effects of captopril on ischemic events after myocardial infarction. Results of the Survival and Ventricular Enlargement trial. Circulation. 1994;90:1731–8.
715. Eagle KA, Guyton RA, Davidoff R, et al. ACC/AHA 2004 guideline update for coronary artery bypass graft surgery: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (Committee to Update the 1999 Guidelines for Coronary Artery Bypass Graft Surgery). Available at: http://www.acc.org/clinical/guidelines/cabg/cabg.pdf. Accessed June 30, 2005.
716. Di Carli MF, Asgarzadie F, Schelbert HR, et al. Quantitative relation between myocardial viability and improvement in heart failure symptoms after revascularization in patients with ischemic cardiomyopathy. Circulation. 1995;92:3436–44.
717. Elefteriades JA, Tolis G Jr., Levi E, et al. Coronary artery bypass grafting in severe left ventricular dysfunction: excellent survival with improved ejection fraction and functional state. J Am Coll Cardiol. 1993;22:1411–7.
718. Pagano D, Bonser RS, Townend JN, et al. Predictive value of dobutamine echocardiography and positron emission tomography in identifying hibernating myocardium in patients with postischaemic heart failure. Heart. 1998;79:281–8.
719. Baker DW, Jones R, Hodges J, et al. Management of heart failure. III. The role of revascularization in the treatment of patients with moderate or severe left ventricular systolic dysfunction. JAMA. 1994;272:1528–34.
720. Fuster V, Ryden LE, Cannom DS, et al. ACC/AHA/ESC 2006 Guidelines for the Management of Patients with Atrial Fibrillation: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines and the European Society of Cardiology Committee for Practice Guidelines (Writing Committee to Revise the 2001 Guidelines for the Management of Patients With Atrial Fibrillation): developed in collaboration with the European Heart Rhythm Association and the Heart Rhythm Society. Circulation. 2006;114:e257–354.

721. Stevenson WG, Stevenson LW. Atrial fibrillation in heart failure [editorial; comment]. N Engl J Med. 1999;341:910–1.
722. Dries DL, Exner DV, Gersh BJ, et al. Atrial fibrillation is associated with an increased risk for mortality and heart failure progression in patients with asymptomatic and symptomatic left ventricular systolic dysfunction: a retrospective analysis of the SOLVD trials. Studies of Left Ventricular Dysfunction. J Am Coll Cardiol. 1998;32:695–703.
723. Pardaens K, Van Cleemput J, Vanhaecke J, et al. Atrial fibrillation is associated with a lower exercise capacity in male chronic heart failure patients. Heart. 1997;78:564–8.
724. Hasenfuss G, Holubarsch C, Hermann HP, et al. Influence of the force-frequency relationship on haemodynamics and left ventricular function in patients with non-failing hearts and in patients with dilated cardiomyopathy. Eur Heart J. 1994;15:164–70.
725. Kass DA. Force-frequency relation in patients with left ventricular hypertrophy and failure. Basic Res Cardiol. 1998;93 Suppl 1:108–16.
726. Yu CM, Sanderson JE. Right and left ventricular diastolic function in patients with and without heart failure: effect of age, sex, heart rate, and respiration on Doppler-derived measurements. Am Heart J. 1997;134:426–34.
727. Komamura K, Shannon RP, Pasipoularides A, et al. Alterations in left ventricular diastolic function in conscious dogs with pacing-induced heart failure. J Clin Invest. 1992;89:1825–38.
728. Van den Berg MP, Tuinenburg AE, van Veldhuisen DJ, et al. Cardioversion of atrial fibrillation in the setting of mild to moderate heart failure. Int J Cardiol. 1998;63:63–70.
729. Crijns HJ, Van den Berg MP, Van Gelder IC, et al. Management of atrial fibrillation in the setting of heart failure. Eur Heart J. 1997;18 Suppl C:C45–9.
730. Shivkumar K, Jafri SM, Gheorghiade M. Antithrombotic therapy in atrial fibrillation: a review of randomized trials with special reference to the Stroke Prevention in Atrial Fibrillation II (SPAF II) Trial. Prog Cardiovasc Dis. 1996;38:337–42.
731. Botker HE, Toft P, Klitgaard NA, et al. Influence of physical exercise on serum digoxin concentration and heart rate in patients with atrial fibrillation. Br Heart J. 1991;65:337–41.
732. Deedwania PC, Singh BN, Ellenbogen K, et al., for the Department of Veterans Affairs CHF-STAT Investigators. Spontaneous conversion and maintenance of sinus rhythm by amiodarone in patients with heart failure and atrial fibrillation: observations from the veterans affairs congestive heart failure survival trial of antiarrhythmic therapy (CHF-STAT). Circulation. 1998;98:2574–9.
733. Wood MA, Brown-Mahoney C, Kay GN, et al. Clinical outcomes after ablation and pacing therapy for atrial fibrillation: a meta-analysis. Circulation. 2000;101:1138–44.
734. Ozcan C, Jahangir A, Friedman PA, et al. Long-term survival after ablation of the atrioventricular node and implantation of a permanent pacemaker in patients with atrial fibrillation. N Engl J Med. 2001; 344:1043–51.
735. Ozcan C, Jahangir A, Friedman PA, et al. Significant effects of atrioventricular node ablation and pacemaker implantation on left ventricular function and long-term survival in patients with atrial fibrillation and left ventricular dysfunction. Am J Cardiol. 2003;92: 33–7.
736. Boos CJ, Carlsson J, More RS. Rate or rhythm control in persistent atrial fibrillation? QJM. 2003;96:881–92.
737. Naccarelli GV, Rinkenberger RL, Dougherty AH, et al. Adverse effects of amiodarone. Pathogenesis, incidence and management. Med Toxicol Adverse Drug Exp. 1989;4:246–53.
738. Greene HL, Graham EL, Werner JA, et al. Toxic and therapeutic effects of amiodarone in the treatment of cardiac arrhythmias. J Am Coll Cardiol. 1983;2:1114–28.
739. Fuster V, Gersh BJ, Giuliani ER, et al. The natural history of idiopathic dilated cardiomyopathy. Am J Cardiol. 1981;47:525–31.
740. Stratton JR, Nemanich JW, Johannessen KA, et al. Fate of left ventricular thrombi in patients with remote myocardial infarction or idiopathic cardiomyopathy. Circulation. 1988;78:1388–93.
741. Jafri SM. Hypercoagulability in heart failure. Semin Thromb Hemost. 1997;23:543–5.
742. Dunkman WB, Johnson GR, Carson PE, et al., for the V-HeFT VA Cooperative Studies Group. Incidence of thromboembolic events in congestive heart failure. Circulation. 1993;87:VI94–101.
743. Dunkman WB. Thromboembolism and antithrombotic therapy in congestive heart failure. J Cardiovasc Risk. 1995;2:107–17.
744. Cioffi G, Pozzoli M, Forni G, et al. Systemic thromboembolism in chronic heart failure. A prospective study in 406 patients. Eur Heart J. 1996;17:1381–9.
745. Baker DW, Wright RF. Management of heart failure. IV. Anticoagulation for patients with heart failure due to left ventricular systolic dysfunction. JAMA. 1994;272:1614–8.
746. Katz SD. Left ventricular thrombus and the incidence of thromboembolism in patients with congestive heart failure: can clinical factors identify patients at increased risk? J Cardiovasc Risk. 1995;2:97–102.
747. Al Khadra AS, Salem DN, Rand WM, et al. Warfarin anticoagulation and survival: a cohort analysis from the Studies of Left Ventricular Dysfunction. J Am Coll Cardiol. 1998;31:749–53.
748. Kilborn MJ, Karasik PE, Fisher SG, Domanski MJ, Singh SN, Fletcher RD. Anticoagulation in patients with congestive heart failure: evidence for lack of mortality benefit (abstr). Circulation 1999;100 Suppl 1:I-537.
749. Dries DL, Domanski MJ, Waclawiw MA, et al. Effect of antithrombotic therapy on risk of sudden coronary death in patients with congestive heart failure. Am J Cardiol. 1997;79:909–13.
750. Stratton JR, Resnick AD. Increased embolic risk in patients with left ventricular thrombi. Circulation. 1987;75:1004–11.
751. Philbin EF, Santella RN, Rocco TA Jr. Angiotensin-converting enzyme inhibitor use in older patients with heart failure and renal dysfunction. J Am Geriatr Soc. 1999;47:302–8.
752. Alpert MA. Cardiovascular factors influencing survival in dialysis patients. Adv Perit Dial. 1996;12:110–9:110–9.
753. Besarab A, Bolton WK, Browne JK, et al. The effects of normal as compared with low hematocrit values in patients with cardiac disease who are receiving hemodialysis and epoetin. N Engl J Med. 1998; 339:584–90.
754. Biasioli S, Barbaresi F, Barbiero M, et al. Intermittent venovenous hemofiltration as a chronic treatment for refractory and intractable heart failure. ASAIO J. 1992;38:M658–63.
755. Weber KT, Wilson JR, Janicki JS, et al. Exercise testing in the evaluation of the patient with chronic cardiac failure. Am Rev Respir Dis. 1984;129:S60–S62.
756. Singh SN, Fisher SG, Deedwania PC, et al., for the Congestive Heart Failure-Survival Trial of Antiarrhythmic Therapy (CHF-STAT) Investigators. Pulmonary effect of amiodarone in patients with heart failure (Veterans Affairs Cooperative Study No. 320). J Am Coll Cardiol. 1997;30:514–7.
757. Sparano JA. Doxorubicin/taxane combinations: cardiac toxicity and pharmacokinetics. Semin Oncol. 1999;26:14–9.
758. Ibrahim NK, Hortobagyi GN, Ewer M, et al. Doxorubicin-induced congestive heart failure in elderly patients with metastatic breast cancer, with long-term follow-up: the M.D. Anderson experience. Cancer Chemother Pharmacol. 1999;43:471–8.
759. Dieras V. Taxanes in combination with doxorubicin in the treatment of metastatic breast cancer. Semin Oncol. 1998;25:18–22.
760. Shapiro CL, Hardenbergh PH, Gelman R, et al. Cardiac effects of adjuvant doxorubicin and radiation therapy in breast cancer patients. J Clin Oncol. 1998;16:3493–501.
761. Hortobagyi GN. Anthracyclines in the treatment of cancer. An overview. Drugs. 1997;54 Suppl 4:1–7.
762. Schaadt B, Kelbaek H. Age and left ventricular ejection fraction identify patients with advanced breast cancer at high risk for development of epirubicin-induced heart failure. J Nucl Cardiol. 1997;4:494–501.
763. McNeil C. Herceptin raises its sights beyond advanced breast cancer [news]. J Natl Cancer Inst. 1998;90:882–3.
764. Feldman AM, Lorell BH, Reis SE. Trastuzumab in the treatment of metastatic breast cancer: anticancer therapy versus cardiotoxicity. Circulation. 2000;102:272–4.
765. Arsenian MA. Cardiovascular sequelae of therapeutic thoracic radiation. Prog Cardiovasc Dis. 1991;33:299–311.
766. Meinardi MT, van der Graaf WT, van Veldhuisen DJ, et al. Detection of anthracycline-induced cardiotoxicity. Cancer Treat Rev. 1999;25:237–47.
767. Swain SM, Whaley FS, Gerber MC, et al. Delayed administration of dexrazoxane provides cardioprotection for patients with advanced breast cancer treated with doxorubicin-containing therapy. J Clin Oncol. 1997;15:1333–40.

768. Wiseman LR, Spencer CM. Dexrazoxane. A review of its use as a cardioprotective agent in patients receiving anthracycline-based chemotherapy. Drugs. 1998;56:385–403.
769. Grumbach IM, Heermann K, Figulla HR. Low prevalence of hepatitis C virus antibodies and RNA in patients with myocarditis and dilated cardiomyopathy. Cardiology. 1998;90:75–8.
770. Frustaci A, Calabrese F, Chimenti C, et al. Lone hepatitis C virus myocarditis responsive to immunosuppressive therapy. Chest. 2002; 122:1348–56.
771. Frustaci A, Chimenti C, Calabrese F, et al. Immunosuppressive therapy for active lymphocytic myocarditis: virological and immunologic profile of responders versus nonresponders. Circulation. 2003; 107:857–63.
772. Lipshultz SE. Dilated cardiomyopathy in HIV-infected patients. N Engl J Med. 1998;339:1153–5.
773. Lipshultz SE, Easley KA, Orav EJ, et al., for the Pediatric Pulmonary and Cardiac Complications of Vertically Transmitted HIV Infection (P2C2 HIV) Study Group. Left ventricular structure and function in children infected with human immunodeficiency virus: the prospective P2C2 HIV Multicenter Study. Circulation. 1998;97:1246–56.
774. Lewis W, Grupp IL, Grupp G, et al. Cardiac dysfunction occurs in the HIV-1 transgenic mouse treated with zidovudine. Lab Invest. 2000;80:187–97.
775. Barbaro G, Fisher SD, Lipshultz SE. Pathogenesis of HIV-associated cardiovascular complications. Lancet Infect Dis. 2001;1:115–24.
776. Horwich TB, Fonarow GC, Hamilton MA, et al. Anemia is associated with worse symptoms, greater impairment in functional capacity and a significant increase in mortality in patients with advanced heart failure. J Am Coll Cardiol. 2002;39:1780–6.
777. Al-Ahmad A, Rand WM, Manjunath G, et al. Reduced kidney function and anemia as risk factors for mortality in patients with left ventricular dysfunction. J Am Coll Cardiol. 2001;38:955–62.
778. Silverberg DS, Wexler D, Blum M, et al. The use of subcutaneous erythropoietin and intravenous iron for the treatment of the anemia of severe, resistant congestive heart failure improves cardiac and renal function and functional cardiac class, and markedly reduces hospitalizations. J Am Coll Cardiol. 2000;35:1737–44.
779. Silverberg DS, Wexler D, Sheps D, et al. The effect of correction of mild anemia in severe, resistant congestive heart failure using subcutaneous erythropoietin and intravenous iron: a randomized controlled study. J Am Coll Cardiol. 2001;37:1775–80.
780. Mancini DM, Katz SD, Lang CC, et al. Effect of erythropoietin on exercise capacity in patients with moderate to severe chronic heart failure. Circulation. 2003;107:294–9.
781. Krumholz HM, Phillips RS, Hamel MB, et al. Resuscitation preferences among patients with severe congestive heart failure: results from the SUPPORT project. Study to Understand Prognoses and Preferences for Outcomes and Risks of Treatments. Circulation. 1998;98:648–55.
782. Wachter RM, Luce JM, Hearst N, et al. Decisions about resuscitation: inequities among patients with different diseases but similar prognoses. Ann Intern Med. 1989;111:525–32.
783. Greco PJ, Schulman KA, Lavizzo-Mourey R, et al. The Patient Self-Determination Act and the future of advance directives. Ann Intern Med. 1991;115:639–43.
784. Stevenson LW. Rites and responsibility for resuscitation in heart failure: tread gently on the thin places [editorial; comment]. Circulation. 1998;98:619–22.
785. The SUPPORT Principal Investigators. A controlled trial to improve care for seriously ill hospitalized patients. The study to understand prognoses and preferences for outcomes and risks of treatments (SUPPORT) [published erratum appears in JAMA 1996;275:1232]. JAMA. 1995;274:1591–8.
786. Borggrefe M, Chen X, Martinez-Rubio A, et al. The role of implantable cardioverter defibrillators in dilated cardiomyopathy. Am Heart J. 1994;127:1145–50.
787. AGS Ethics Committee. The care of dying patients: a position statement from the American Geriatrics Society. J Am Geriatr Soc. 1995;43:577–8.
788. Gibbs JS, McCoy AS, Gibbs LM, et al. Living with and dying from heart failure: the role of palliative care. Heart. 2002;88 Suppl 2:ii36–9.
789. Fox E, Landrum-McNiff K, Zhong Z, et al., for the SUPPORT Investigators. Evaluation of prognostic criteria for determining hospice eligibility in patients with advanced lung, heart, or liver disease. Study to Understand Prognoses and Preferences for Outcomes and Risks of Treatments. JAMA. 1999;282:1638–45.
790. Standards and Accreditation Committee, Medical Guidelines Task Force, Stuart B, Alexander C, Arenella C, et al. Medical guidelines for determining prognosis in selected noncancer diseases. Alexandria, VA: National Hospice Organization. 1996;1–28.
791. Konstam M, Dracup K, Baker D, et al. Heart failure: evaluation and care of patients with left-ventricular systolic dysfunction. 1994; Clinical Practice Guideline No. 11, AHCPR publication No. 94–1612.
792. Philbin EF, Rocco TA Jr., Lindenmuth NW, et al. Clinical outcomes in heart failure: report from a community hospital-based registry. Am J Med. 1999;107:549–55.
793. Krumholz HM, Wang Y, Parent EM, et al. Quality of care for elderly patients hospitalized with heart failure. Arch Intern Med. 1997;157: 2242–7.
794. Kahn KL, Rogers WH, Rubenstein LV, et al. Measuring quality of care with explicit process criteria before and after implementation of the DRG-based prospective payment system. JAMA. 1990;264: 1969–73.
795. Rubenstein LV, Kahn KL, Reinisch EJ, et al. Changes in quality of care for five diseases measured by implicit review, 1981 to 1986. JAMA. 1990;264:1974–9.
796. Oddone EZ, Weinberger M, Horner M, et al., for the Veterans Affairs Cooperative Studies in Health Services Group on Primary Care and Hospital Readmissions. Classifying general medicine readmissions. Are they preventable? J Gen Intern Med. 1996;11:597–607.
797. Weingarten S, Riedinger M, Conner L, et al. Reducing lengths of stay in the coronary care unit with a practice guideline for patients with congestive heart failure. Insights from a controlled clinical trial. Med Care. 1994;32:1232–43.
798. National Health Service Centre for Reviews and Dissemination. Getting evidence into practice. Effective Health Care. 1999;5:1–16.
799. Oxman AD, Thomson MA, Davis DA, et al. No magic bullets: a systematic review of 102 trials of interventions to improve professional practice. CMAJ. 1995;153:1423–31.
800. Bero LA, Grilli R, Grimshaw JM, et al., for the Cochrane Effective Practice and Organization of Care Review Group. Closing the gap between research and practice: an overview of systematic reviews of interventions to promote the implementation of research findings. BMJ. 1998;317:465–8.
801. Soumerai SB, Avorn J. Principles of educational outreach ('academic detailing') to improve clinical decision making. JAMA. 1990;263:549–56.
802. Rich MW. Heart failure disease management: a critical review. J Card Fail. 1999;5:64–75.
803. Rich MW, Nease RF. Cost-effectiveness analysis in clinical practice: the case of heart failure. Arch Intern Med. 1999;159:1690–700.
804. Marshall MN, Shekelle PG, Leatherman S, et al. The public release of performance data: what do we expect to gain? A review of the evidence. JAMA. 2000;283:1866–74.
805. Chin MH, Friedmann PD, Cassel CK, et al. Differences in generalist and specialist physicians' knowledge and use of angiotensin-converting enzyme inhibitors for congestive heart failure. J Gen Intern Med. 1997;12:523–30.
806. Edep ME, Shah NB, Tateo IM, et al. Differences between primary care physicians and cardiologists in management of congestive heart failure: relation to practice guidelines. J Am Coll Cardiol. 1997;30:518–26.
807. Baker DW, Hayes RP, Massie BM, et al. Variations in family physicians' and cardiologists' care for patients with heart failure. Am Heart J. 1999;138:826–34.
808. Reis SE, Holubkov R, Edmundowicz D, et al. Treatment of patients admitted to the hospital with congestive heart failure: specialty-related disparities in practice patterns and outcomes. J Am Coll Cardiol. 1997;30:733–8.
809. Philbin EF, Weil HF, Erb TA, et al. Cardiology or primary care for heart failure in the community setting: process of care and clinical outcomes. Chest. 1999;116:346–54.
810. Auerbach AD, Hamel MB, Davis RB, et al., for the SUPPORT Investigators. Resource use and survival of patients hospitalized with congestive heart failure: differences in care by specialty of the attending physician. Study to Understand Prognoses and Preferences for Outcomes and Risks of Treatments. Ann Intern Med. 2000;132: 191–200.

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## APPENDIX 1. AUTHOR RELATIONSHIPS WITH INDUSTRY—ACC/AHA 2005 GUIDELINES FOR THE DIAGNOSIS AND MANAGEMENT OF CHRONIC HEART FAILURE IN THE ADULT

| Committee Member | Research Grant | Speakers' Bureau | Stock Ownership | Board of Directors | Consultant/ Advisory Member |
|---|---|---|---|---|---|
| Dr. William T. Abraham | • Amgen<br>• Biosite<br>• Biotronik<br>• Cardio Dynamics International<br>• Guidant<br>• Medtronic<br>• Myogen<br>• Orqis Medical<br>• Otsuka Maryland Research Institute<br>• Scios<br>• Vasogen<br>• Yamanouchi | • GlaxoSmithKline<br>• Guidant<br>• Medtronic<br>• Merck<br>• Pfizer<br>• Scios<br>• St. Jude Medical | None | None | None |
| Dr. Marshall H. Chin | None | None | None | None | None |
| Dr. Arthur M. Feldman | • Amgen<br>• AstraZeneca<br>• GlaxoSmithKline<br>• Guidant<br>• Medtronic<br>• Pfizer<br>• Scios<br>• Vasomedical | • AstraZeneca<br>• GlaxoSmithKline<br>• Guidant<br>• Johnson & Johnson<br>• Medtronic<br>• Vasomedical | None | None | None |
| Dr. Gary S. Francis | None | None | None | None | None |
| Dr. Theodore G. Ganiats | None | None | None | None | None |
| Dr. Sharon Ann Hunt | None | None | None | None | None |
| Dr. Mariell Jessup | None | None | None | None | • ACORN<br>• Medtronic<br>• GlaxoSmithKline |
| Dr. Marvin A. Konstam | • GlaxoSmithKline | • AstraZeneca<br>• GlaxoSmithKline<br>• Merck<br>• Novartis | None | None | • AstraZeneca<br>• GlaxoSmithKline<br>• Merck<br>• Novartis |
| Dr. Donna M. Mancini | None | None | None | None | None |
| Dr. Keith A. Michl | None | None | None | None | None |
| Dr. John A. Oates | • McNeil<br>• Merck | None | None | None | • McNeil<br>• Merck |
| Dr. Peter S. Rahko | • Bristol-Myers Squibb<br>• Myogen<br>• Novartis | • Boehringer-Ingelheim<br>• Novartis<br>• Pfizer | None | None | • GlaxoSmithKline |
| Dr. Marc A. Silver | • Pfizer | • GlaxoSmithKline | • Cardiodynamics | None | None |
| Dr. Lynne Warner Stevenson | • Medtronic | None | None | None | • Medtronic<br>• Scios |
| Dr. Clyde W. Yancy | • NitroMed<br>• Scios | • GlaxoSmithKline<br>• Medtronic<br>• Novartis<br>• Pfizer<br>• Scios | None | None | • GlaxoSmithKline<br>• Medtronic<br>• Scios |

## APPENDIX 2. PEER REVIEWER RELATIONSHIPS WITH INDUSTRY—ACC/AHA 2005 GUIDELINES 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<br>• Otzuka<br>• Sigma Tau | • Pfizer | None | • GlaxoSmithKline<br>• Medtronic<br>• Otzuka<br>• Sigma Tau |
| Dr. Jonathan L. Halperin | Official Reviewer—ACCF/AHA Task Force Lead Review | None | • AstraZeneca<br>• Bristol-Myers Squibb/ Sanofi Partnership | None | • AstraZeneca<br>• Bayer AG<br>• Boehringer Ingelheim<br>• Bristol-Myers Squibb/ Sanofi Partnership |
| Dr. Jagat Narula | Official Reviewer—AHA | None | None | None | None |
| Dr. Milton Packer | Official Reviewer—ACCF/AHA | None | None | • Discovery Laboratories<br>• Titan Pharmaceuticals | • Abbott<br>• Actelion<br>• AstraZeneca<br>• Cardiodynamics<br>• Discovery Laboratories<br>• GlaxoSmithKline<br>• Orion Pharmaceuticals<br>• Titan Pharmaceuticals<br>• Yamanouchi |
| Dr. Ileana L. Pina | Official Reviewer—AHA | • Biosite<br>• Centers for Medicare and Medicaid Services<br>• National Institutes of Health | • AstraZeneca<br>• GlaxoSmithKline<br>• Novartis<br>• Pfizer | None | • AstraZeneca<br>• Food and Drug Administration–Center for Devices and Radiological Health |
| 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 | • AstraZeneca<br>• Bristol-Myers Squibb<br>• Novartis | • Cardiodynamics | • Bristol-Myers Squibb<br>• Cardiodynamics<br>• Novartis |
| Nancy M. Albert, CNS | Content Reviewer—AHA HF and Transplantation Committee | None | • GlaxoSmithKline<br>• Medtronic<br>• Scios Pharmaceuticals | None | • GlaxoSmithKline |
| Dr. Jeffrey L. Anderson | Content Reviewer—Individual Review | None | • Johnson & Johnson Merck<br>• Merck<br>• Merck-Schering-Plough | None | • Johnson & Johnson Merck<br>• Merck<br>• Merck-Schering-Plough |
| Dr. Elliott M. Antman | Content Reviewer—Individual Review | • AstraZeneca<br>• Biosite<br>• Boehringer Mannheim<br>• Bristol-Myers Squibb<br>• Centocor<br>• CV Therapeutics<br>• Dade<br>• Dendrion<br>• Eli Lilly<br>• Genentech<br>• Merck<br>• Millennium<br>• Sanofi-Aventis<br>• Sunol Molecular | None | None | None |
| Dr. Malcolm O. Arnold | Content Reviewer—ACCF HF Data Standards Committee | None | • Aventis<br>• Merck-Frosst<br>• Novartis<br>• Pfizer | None | • Aventis<br>• Merck-Frosst<br>• Novartis<br>• Pfizer |

| Peer Reviewer Name* | Representation | Research Grant | Speakers' Bureau/ Honoraria | Stock Ownership | Consultant/ Advisory Board |
|---|---|---|---|---|---|
| Dr. John P. Boehmer | Content Reviewer—Individual Review | • Acorn Cardiovascular<br>• Amgen<br>• Cardiovascular Bio Therapeutics<br>• Guidant<br>• Medtronic<br>• Myogen<br>• Orion Pharmaceuticals | None | None | None |
| Dr. Michael R. Bristow | Content Reviewer—Individual Review | None | None | None | • AstraZeneca<br>• Cardiac Dimensions<br>• Covalent<br>• C2R<br>• CVRx<br>• Genzyme<br>• GlaxoSmithKline<br>• Guidant<br>• Merck<br>• Mitsubishi<br>• Mylan<br>• Myogen<br>• Novartis<br>• Scios Pharmaceuticals |
| Dr. Alfred E. Buxton | Content Reviewer—ACCF/AHA Ventricular Arrhythmias and Sudden Cardiac Death Guideline Committee | • Guidant<br>• Medtronic<br>• 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—ACCF HF Performance Measures Committee | None | None | None | None |
| Dr. Michael P. Cinquegrani | Content Reviewer—ACCF HF Data Standards Committee | None | None | • Medtronic<br>• Pfizer | None |
| Dr. Teresa De Marco | Content Reviewer—Individual Review | • Scios Pharmaceuticals | • Guidant<br>• Medtronic<br>• Scios Pharmaceuticals | None | • Guidant<br>• Medtronic<br>• Scios Pharmaceuticals |
| Dr. Gordon A. Ewy | Content Reviewer—ACCF/AHA Coronary Artery Bypass Graft Surgery Guideline Writing Committee | None | • AstraZeneca<br>• GlaxoSmithKline<br>• Kos<br>• Merck<br>• Pfizer<br>• Schering-Plough<br>• Wyeth-Ayerst | None | None |
| Dr. Gregg C. Fonarow | Content Reviewer—AHA Quality of Care and Outcomes Committee | • Amgen<br>• Biosite<br>• Bristol-Myers Squibb<br>• GlaxoSmithKline<br>• Guidant<br>• Medtronic<br>• Merck<br>• Pfizer<br>• Scios Pharmaceuticals | • Amgen<br>• Biosite<br>• Bristol-Myers Squibb<br>• GlaxoSmithKline<br>• Guidant<br>• Medtronic<br>• Merck<br>• Pfizer<br>• Scios Pharmaceuticals | None | • Amgen<br>• Biosite<br>• Bristol-Myers Squibb<br>• GlaxoSmithKline<br>• Guidant<br>• Medtronic<br>• Merck<br>• Pfizer<br>• Scios Pharmaceuticals |
| Dr. Michael M. Givertz | Content Reviewer—AHA Committee on HF and Transplantation | None | None | None | None |

| Peer Reviewer Name* | Representation | Research Grant | Speakers' Bureau/ Honoraria | Stock Ownership | Consultant/ Advisory Board |
|---|---|---|---|---|---|
| Dr. David C. Goff | Content Reviewer—AHA Quality of Care and Outcomes Committee | None | • Pfizer | None | • Johnson & Johnson<br>• Pfizer |
| Dr. Edward P. Havranek | Content Reviewer—ACCF HF Data Standards Committee | None | None | None | None |
| Dr. Paul A. Heidenreich | Content Reviewer—ACCF HF Data Standards Committee | None | None | None | None |
| Dr. Mark A. Hlatky | Content Reviewer—ACCF HF Performance Measures Committee | None | None | None | None |
| Dr. Judith S. Hochman | Content Reviewer—ACCF/AHA ST-Elevation Myocardial Infarction Guideline Writing Committee | • Arginox<br>• Eli Lilly | None | None | • Datascope<br>• Diachii<br>• Millenium<br>• Sanofi-Aventis<br>• Proctor & Gamble |
| Dr. Marrick L. Kuckin | Content Reviewer—Individual Review | • AstraZeneca<br>• Myogen<br>• Vasogen | • AstraZeneca<br>• Myogen | None | • AstraZeneca |
| 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 | • Berlex<br>• Bristol-Myers Squibb/Sanofi<br>• Millenium<br>• Schering-Plough | None | • Medtronic | None |
| Dr. Eric N. Prystowsky | Content Reviewer—ACCF/AHA/ESC Atrial Fibrillation | None | None | None | • Guidant |
| Dr. Andrew L. Smith | Content Reviewer—ACCF HF Performance Measures Committee | • Guidant<br>• Medtronic<br>• Nitromed | • Guidant<br>• Medtronic | None | None |
| 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 | • AstraZeneca | None | None | • AstraZeneca<br>• Bristol-Myers Squibb/ Sanofi<br>• Merck<br>• Novartis<br>• Servier |

| Peer Reviewer Name* | Representation | Research Grant | Speakers' Bureau/ Honoraria | Stock Ownership | Consultant/ Advisory Board |
|---|---|---|---|---|---|
| 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<br>• Medtronic<br>• Myogen<br>• Novocardia<br>• Pfizer<br>• Scios Pharmaceuticals | None | None | None |
| Dr. Mandeep R. Mehra | Organizational Reviewer—International Society for Heart and Lung Transplantation | • AstraZeneca<br>• Biosite Diagnostics<br>• Guidant<br>• Medtronic<br>• Merck<br>• Scios | • AstraZeneca<br>• Biosite Diagnostics<br>• Guidant<br>• Medtronic<br>• Merck<br>• Novartis<br>• Scios | • Hommed | • AstraZeneca<br>• Biosite Diagnostics<br>• Guidant<br>• Medtronic<br>• Merck<br>• Novartis<br>• Scios |
| Dr. Alan Miller | Organizational Reviewer—Heart Failure Society of America | • Amgen<br>• AstraZeneca<br>• GlaxoSmithKline<br>• Myogen<br>• NitroMed<br>• Novartis<br>• Pfizer | • AstraZeneca<br>• Bristol-Myers Squibb/ Sanofi<br>• GlaxoSmithKline<br>• Novartis<br>• Pfizer<br>• Wyeth | None | • GlaxoSmithKline<br>• Pfizer |
| Dr. K. Vijayaraghavan | Organizational Reviewer—American College of Chest Physicians | • Amgen<br>• AstraZeneca<br>• Cardiodynamics<br>• Kos<br>• Merck-Schering-Plough<br>• Myogen<br>• Pfizer | • GlaxoSmithKline<br>• Guidant<br>• Merck<br>• Medtronic<br>• Novartis<br>• Pfizer<br>• Scios Pharmaceuticals | None | None |

This table represents the relationships of peer reviewers with industry that were disclosed at the time of peer review of this guideline. It does not necessarily reflect relationships with industry at the time of publication.

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

## APPENDIX 3. REMATCH TRIAL ABBREVIATIONS

| | | | |
|---|---|---|---|
| ACCF | American College of Cardiology | HDL | high-density lipoprotein |
| ACE | angiotensin converting enzyme | HF | heart failure |
| ACEI | angiotensin converting enzyme inhibitor | HIV | human immunodeficiency virus |
| AHA | American Heart Association | ICD | implantable cardioverter-defibrillator |
| ARB | angiotensin II receptor blocker | LBBB | left bundle-branch block |
| ATPase | adenosine triphosphatase | LV | left ventricular |
| BNP | B-type natriuretic peptide | LVEF | left ventricular ejection fraction |
| CPAP | continuous positive airway pressure | LVH | left ventricular hypertrophy |
| CRT | cardiac resynchronization therapy | MI | myocardial infarction |
| DCM | dilated cardiomyopathy | Na+-K+ | sodium-potassium |
| DIG | Digitalis Investigation Group | NYHA | New York Heart Association |
| EF | ejection fraction | RBBB | right bundle-branch block |
| EPO | erythropoietin | REMATCH | Randomized Evaluation of Mechanical Assistance for the Treatment of Congestive Heart Failure |
| FHx CM | family history of cardiomyopathy | RVEF | right ventricular ejection fraction |
| HCM | hypertrophic cardiomyopathy | STICH | Surgical Treatment for Ischemic Heart Failure |
| HCV | hepatitis C viral infection | VT | ventricular tachycardia |

## APPENDIX 4. AUTHOR RELATIONSHIPS WITH INDUSTRY AND OTHER ENTITIES—2009 FOCUSED UPDATE: ACCF/AHA GUIDELINES FOR THE DIAGNOSIS AND MANAGEMENT OF HEART FAILURE IN ADULTS

| Committee Member | Consultant | Speaker | Ownership/ Partnership/ Principal | Research | Institutional, Organizational or Other Financial Benefit | Expert Witness |
|---|---|---|---|---|---|---|
| Dr. Mariell Jessup *(Chair)* | • Acorn<br>• CardioMEMS<br>• GlaxoSmithKline<br>• Medtronic<br>• Scios<br>• Ventracor | None | None | None | None | None |
| Dr. William T. Abraham | • Arrow International<br>• AstraZeneca<br>• BioEnergy<br>• Boehringer Ingelheim<br>• CardioKine<br>• CardioKinetix<br>• CardioMEMS*<br>• CHF Solutions<br>• Department of Veterans Affairs Cooperative Studies Program<br>• Edwards Lifesciences<br>• Inovise<br>• Medtronic*<br>• Merck<br>• National Institutes of Health<br>• Novartis<br>• Paracor<br>• Pfizer<br>• ResMed<br>• Respironics<br>• Scios<br>• St. Jude Medical*<br>• Sunshine Heart | • Amgen<br>• AstraZeneca<br>• Boehringer Ingelheim<br>• CHF Solutions<br>• GlaxoSmithKline<br>• Guidant<br>• Medtronic*<br>• Merck<br>• Novartis<br>• Pfizer<br>• ResMed<br>• Respironics<br>• Scios<br>• St. Jude Medical* | None | • Heart Failure Society of America<br>• Medtronic*<br>• National Institutes of Health<br>• Paracor*<br>• St. Jude Medical* | None | None |
| Dr. Donald E. Casey | None | None | None | None | None | None |
| Dr. Arthur M. Feldman | • Alinea Pharmaceutical<br>• Arca Discovery | None | • Cardiokine* | None | • Cardiokine* | None |
| Dr. Gary S. Francis | • Biosite<br>• Boehringer Ingelheim<br>• GlaxoSmithKline<br>• Medtronic<br>• NitroMed<br>• Otsuka | None | None | None | None | None |
| Dr. Theodore G. Ganiats | None | None | None | None | None | None |
| Dr. Marvin A. Konstam | • AstraZeneca<br>• Cardiokine<br>• GlaxoSmithKline<br>• Merck*<br>• Nitromed<br>• Novartis*<br>• Otsuka*<br>• Sanofi | • Otsuka* | • Orqis* | • GlaxoSmithKline<br>• Nitromed<br>• Otsuka* | None | None |

| Committee Member | Consultant | Speaker | Ownership/ Partnership/ Principal | Research | Institutional, Organizational or Other Financial Benefit | Expert Witness |
|---|---|---|---|---|---|---|
| Dr. Donna M. Mancini | • Acorn<br>• Celladon | None | None | None | None | None |
| Dr. Peter S. Rahko | • Breast Cancer International Research Group | • Boehringer Ingelheim<br>• GlaxoSmithKline<br>• Novartis | None | • Enoxsive Pharmaceuticals | None | • Depostion, Plaintiff, Myocardial Infarction Post Motor Vehicle Accident |
| Dr. Marc A. Silver | None | • GlaxoSmithKline<br>• Johnson & Johnson | None | None | None | None |
| Dr. Lynne Warner Stevenson | None | None | None | • CardioMEMS<br>• Medtronic | None | • CardioMEMS<br>• Medtronic |
| Dr. Clyde W. Yancy | • GlaxoSmithKline*<br>• Nitromed<br>• Scios<br>• Arca Discovery* | • GlaxoSmithKline*<br>• Novartis | None | • GlaxoSmithKline<br>• Medtronic<br>• Nitromed<br>• Scios | None | None |

This table represents the relevant relationships of committee members with industry and other entities that were reported orally at the initial writing committee meeting and updated in conjunction with all meetings and conference calls of the writing committee during the document development process. It does not necessarily reflect relationships with industry at the time of publication. A person is deemed to have a significant interest in a business if the interest represents ownership of 5% or more of the voting stock or share of the business entity, or ownership of $10 000 or more of the fair market value of the business entity; or if funds received by the person from the business entity exceed 5% of the person's gross income for the previous year. A relationship is considered to be modest if it is less than significant under the preceding definition. Relationships in this table are modest unless otherwise noted.

*Significant (greater than $10 000) relationship.

## APPENDIX 5. REVIEWER RELATIONSHIPS WITH INDUSTRY AND OTHER ENTITIES—2009 FOCUSED UPDATE: ACCF/AHA GUIDELINES FOR THE DIAGNOSIS AND MANAGEMENT OF HEART FAILURE IN ADULTS

| Peer Reviewer | Representation | Consultant | Speaker | Ownership/ Partnership/ Principal | Research | Institutional, Organizational or Other Financial Benefit | Expert Witness |
|---|---|---|---|---|---|---|---|
| Dr. Steven M. Ettinger | Official—American College of Cardiology/American Heart Association Task Force on Practice Guidelines | None | None | None | None | None | None |
| Dr. Gregg G. Fonarow | Official—American Heart Association | • AstraZeneca<br>• Bristol-Myers Squibb/Sanofi*<br>• GlaxoSmithKline*<br>• Medtronic*<br>• Merck*<br>• Novartis*<br>• Pfizer* | • AstraZeneca<br>• Bristol-Myers Squibb/Sanofi*<br>• GlaxoSmithKline*<br>• Medtronic*<br>• Merck*<br>• Novartis*<br>• Pfizer* | None | None | None | None |
| Dr. G. Harold | Official—American College of Cardiology Board of Trustees | None | None | None | None | None | None |
| Dr. Robert E. Hobbs | Official—American College of Cardiology Board of Governors | None | • Scios* | None | None | None | None |

| Peer Reviewer | Representation | Consultant | Speaker | Ownership/ Partnership/ Principal | Research | Institutional, Organizational or Other Financial Benefit | Expert Witness |
|---|---|---|---|---|---|---|---|
| Dr. Michael R. Zile | Official—American Heart Association | • Bristol-Myers Squibb/Sanofi<br>• Enoxsive<br>• Medtronic<br>• Novartis<br>• Orqis<br>• Ortho Clinical Diagnostic<br>• Synvista | None | None | • Bristol-Myers Squibb/Sanofi<br>• Enoxsive<br>• Medtronic<br>• Novartis<br>• Orqis<br>• Ortho Clinical Diagnostic<br>• Synvista | None | None |
| Dr. Doug Campos-Outcalt | Organizational—American Academy of Family Physicians | None | None | None | None | None | None |
| Dr. Jun R. Chiong | Organizational—American College of Chest Physicians | • Roche Diagnostics | • GlaxoSmithKline | None | None | None | None |
| Dr. Steven Durning | Organizational—American College of Physicians | None | None | None | None | None | None |
| Dr. Kurt Elward | Organizational—American Academy of Family Physicians | None | None | None | None | None | None |
| Dr. Michael Felker | Organizational—Heart Failure Society of America | • Amgen<br>• Boston Scientific<br>• Corthera<br>• Cytokinetics<br>• Geron<br>• XDS | • Amgen<br>• Cytokinetics<br>• Roche Diagnostics | None | None | None | None |
| Dr. David D. Gutterman | Organizational—American College of Chest Physicians | None | None | • Johnson & Johnson* | • National Institutes of Health* | None | None |
| Dr. Charin L. Hanlon | Organizational—American College of Physicians | None | None | None | None | None | None |
| Dr. Thomas F. Koinis | Organizational—American Academy of Family Physicians | None | None | None | None | None | None |
| Dr. Alan B. Miller | Organizational—Heart Failure Society of America | None | • AstraZeneca<br>• Bristol-Myers Squibb<br>• CV Therapeutics<br>• GlaxoSmithKline<br>• Novartis | • CV Therapeutics<br>• Medtronic<br>• Merck | None | None | None |
| Dr. Srinivas Murali | Organizational—International Society of Heart and Lung Transplantation | None | None | None | • Jarvik<br>• Novacardiac<br>• Paracor<br>• Scios<br>• Thoratic<br>• Ventrocor | • Boston Scientific* (salary)<br>• Medtronic* (salary)<br>• St. Jude's* (salary) | None |
| Dr. Nancy M. Albert | Content—American Heart Association Heart Failure and Transplant Committee | • Arca biopharma<br>• GlaxoSmithKline<br>• Medtronic | • GlaxoSmithKline | None | • GlaxoSmithKline*<br>• Medtronic* | None | None |
| Dr. John D. Bisognano | Content—American College of Cardiology Board of Governors | None | None | None | None | None | None |

| Peer Reviewer | Representation | Consultant | Speaker | Ownership/ Partnership/ Principal | Research | Institutional, Organizational or Other Financial Benefit | Expert Witness |
|---|---|---|---|---|---|---|---|
| Dr. Javed Butler | Content—American College of Cardiology Heart Failure and Transplant Committee | None | • Boehringer Ingelheim*<br>• GlaxoSmithKline*<br>• Novartis* | None | None | None | None |
| Dr. David E. Lanfear | Content—American College of Cardiology Heart Failure and Transplant Committee | • Thoratec | None | None | • Merck<br>• Sanofi-Aventis | None | None |
| Dr. Joann Lindenfeld | Content—American Heart Association Heart Failure and Transplant Committee | • Arca biopharma<br>• CV Therapeutics*<br>• Medtronic<br>• Sanofi-Aventis<br>• Takeda | None | None | • Merck<br>• Somalogic | None | None |
| Dr. Wayne L. Miller | Content—American Heart Association Heart Failure and Transplant Committee | None | None | None | None | None | None |
| Dr. Judith E. Mitchell | Content—American Heart Association Heart Failure and Transplant Committee | • GlaxoSmithKline<br>• NitroMed | • GlaxoSmithKline<br>• NitroMed | None | None | None | None |
| Dr. Rick A. Nishimura | Content—American College of Cardiology/American Heart Association Task Force on Practice Guidelines | None | None | None | None | None | None |
| Dr. Donna F. Petruccelli | Content—American College of Cardiology Heart Failure and Transplant Committee | None | None | None | None | None | None |
| Dr. Win Kuang Shen | Content—American Heart Association Heart Failure and Transplant Committee | None | None | None | • Medtronic* | None | None |
| Dr. Lynn G. Tarkington | Content—American College of Cardiology/American Heart Association Task Force on Practice Guidelines | None | None | None | None | None | None |
| Dr. Emily J. Tsai | Content—American College of Cardiology Heart Failure and Transplant Committee | None | None | None | None | None | None |

This table represents the relevant relationships with industry and other entities that were disclosed at the time of peer review. It does not necessarily reflect relationships with industry at the time of publication. A person is deemed to have a significant interest in a business if the interest represents ownership of 5% or more of the voting stock or share of the business entity, or ownership of $10 000 or more of the fair market value of the business entity; or if funds received by the person from the business entity exceed 5% of the person's gross income for the previous year. A relationship is considered to be modest if it is less than significant under the preceding definition. Relationships in this table are modest unless otherwise noted. Names are listed in alphabetical order within each category of review.

*Significant (greater than $10 000) relationship.

# 2009 Focused Update Incorporated Into the ACC/AHA 2005 Guidelines for the Diagnosis and Management of Heart Failure in Adults: A Report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines Developed in Collaboration With the International Society for Heart and Lung Transplantation

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