

ACCF/AHA Practice Guideline: Focused Update

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

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

2009 WRITING GROUP TO REVIEW NEW EVIDENCE AND UPDATE THE 2005 GUIDELINE FOR THE MANAGEMENT OF PATIENTS WITH CHRONIC HEART FAILURE WRITING ON BEHALF OF THE 2005 HEART FAILURE WRITING COMMITTEE

Mariell Jessup, MD, FACC, FAHA, Chair*; William T. Abraham, MD, FACC, FAHA†; Donald E. Casey, MD, MPH, MBA‡; Arthur M. Feldman, MD, PhD, FACC, FAHA§; Gary S. Francis, MD, FACC, FAHA¶; Theodore G. Ganiats, MD||; Marvin A. Konstam, MD, FACC¶¶; Donna M. Mancini, MD#; Peter S. Rahko, MD, FACC, FAHA†; Marc A. Silver, MD, FACC, FAHA**; Lynne Warner Stevenson, MD, FACC, FAHA†; Clyde W. Yancy, MD, FACC, FAHA††

2005 WRITING COMMITTEE MEMBERS

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

TASK FORCE MEMBERS

Sidney C. Smith, Jr, MD, FACC, FAHA, Chair; Alice K. Jacobs, MD, FACC, FAHA, Vice-Chair; Christopher E. Buller, MD, FACC; Mark A. Creager, MD, FACC, FAHA; Steven M. Ettinger, MD, FACC; Harlan M. Krumholz, MD, FACC, FAHA; Frederick G. Kushner, MD, FACC, FAHA; Bruce W. Lytle, MD, FACC, FAHA‡‡; Rick A. Nishimura, MD, FACC, FAHA; Richard L. Page, MD, FACC, FAHA; Lynn G. Tarkington, RN; Clyde W. Yancy, MD, FACC, FAHA

*International Society for Heart and Lung Transplantation Representative.

†American College of Cardiology Foundation/American Heart Association Representative.

‡American College of Physicians Representative.

§Heart Failure Society of America Representative.

||American Academy of Family Physicians Representative.

¶American College of Cardiology Foundation/American Heart Association Performance Measures Liaison.

#Content Expert.

**American College of Chest Physicians Representative.

††American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines Liaison.

‡‡Former Task Force member during the writing effort.

This document is a limited update to the 2005 guideline update and is based on a review of certain evidence, not a full literature review. This document was approved by the American College of Cardiology Foundation Board of Trustees and by the American Heart Association Science Advisory and Coordinating Committee in October 2008.

The American Heart Association requests that this document be cited as follows: Jessup M, Abraham WT, Casey DE, Feldman AM, Francis GS, Ganiats TG, Konstam MA, Mancini DM, Rahko PS, Silver MA, Stevenson LW, Yancy CW, writing on behalf of the 2005 Guideline Update for the Diagnosis and Management of Chronic Heart Failure in the Adult Writing Committee. 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. *Circulation*. 2009;119:000–000.

This article has been copublished in the *Journal of the American College of Cardiology*.

Copies: This document is available on the World Wide Web sites of the American College of Cardiology (www.acc.org) and the American Heart Association (my.americanheart.org). A copy of the document is also available at <http://www.americanheart.org/presenter.jhtml?identifier=3003999> by selecting either the “topic list” link or the “chronological list” link (No. LS-2013). To purchase additional reprints, call 843-216-2533 or e-mail kelle.ramsay@wolterskluwer.com.

Expert peer review of AHA Scientific Statements is conducted at the AHA National Center. For more on AHA statements and guidelines development, visit <http://www.americanheart.org/presenter.jhtml?identifier=3023366>.

Permissions: Multiple copies, modification, alteration, enhancement, and/or distribution of this document are not permitted without the express permission of the American Heart Association. Instructions for obtaining permission are located at <http://www.americanheart.org/presenter.jhtml?identifier=4431>. A link to the “Permission Request Form” appears on the right side of the page.

(*Circulation*. 2009;119:xxx-xxx.)

© 2009 by the American College of Cardiology Foundation and the American Heart Association, Inc.

Circulation is available at <http://circ.ahajournals.org>

DOI: 10.1161/CIRCULATIONAHA.109.192064

TABLE OF CONTENTS

Preamble.....	XXXX
1. Introduction.....	XXXX
1.1. Evidence Review.....	XXXX
1.2. Organization of Committee and Relationships With Industry.....	XXXX
1.3. Review and Approval.....	XXXX
1.4. Stages of Heart Failure: Information From the 2005 Guideline.....	XXXX
3. Initial and Serial Clinical Assessment of Patients	
Presenting With Heart Failure.....	XXXX
3.1. Initial Evaluation of Patients.....	XXXX
3.1.1. Identification of Patients.....	XXXX
3.1.2. Identification of a Structural and Functional Abnormality.....	XXXX
3.1.3.2. Laboratory Testing.....	XXXX
3.2.3. Laboratory Assessment.....	XXXX
3.2.4. Assessment of Prognosis.....	XXXX
4. Therapy.....	XXXX
4.3.1. Patients With Reduced Left Ventricular Ejection Fraction.....	XXXX
4.3.1.1. General Measures.....	XXXX
4.3.1.2.5. Ventricular Arrhythmias and Prevention of Sudden Death.....	XXXX
4.3.1.3.3. Hydralazine and Isosorbide Dinitrate.....	XXXX
4.3.1.3.4. Cardiac Resynchronization Therapy.....	XXXX
4.3.1.5.2. Intermittent Intravenous Positive Inotropic Therapy.....	XXXX
4.4. Patients With Refractory End-Stage Heart Failure (Stage D).....	XXXX
4.4.3. Intravenous Peripheral Vasodilators and Positive Inotropic Agents.....	XXXX
4.5. The Hospitalized Patient (New Section).....	XXXX
4.5.1. Diagnostic Strategies.....	XXXX
4.5.2. Treatment in the Hospital.....	XXXX
4.5.2.1. Diuretics: The Patient With Volume Overload.....	XXXX
4.5.2.2. Vasodilators.....	XXXX
4.5.2.3. Inotropes.....	XXXX
4.5.2.4. Other Considerations.....	XXXX
4.5.3. The Hospital Discharge.....	XXXX
5. Treatment of Special Populations.....	XXXX
6. Patients With Heart Failure Who Have Concomitant Disorders.....	XXXX
6.1.3. Supraventricular Arrhythmias.....	XXXX
Appendix 1.....	XXXX
Appendix 2.....	XXXX
References.....	XXXX

Preamble

A primary challenge in the development of clinical practice guidelines is keeping pace with the stream of new data on

which recommendations are based. In an effort to respond more quickly to new evidence, the American College of Cardiology Foundation/American Heart Association (ACCF/AHA) Task Force on Practice Guidelines has created a “focused update” process to revise the existing guideline recommendations that are affected by the evolving data or opinion. Prior to the initiation of this focused approach, periodic updates and revisions of existing guidelines required up to 3 years to complete. Now, however, new evidence is reviewed in an ongoing fashion to more efficiently respond to important science and treatment trends that could have a major impact on patient outcomes and quality of care. Evidence is reviewed at least twice a year, and updates will be initiated on an as-needed basis as quickly as possible, while maintaining the rigorous methodology that the ACCF and AHA have developed during their more than 20 years of partnership.

These updated guideline recommendations reflect a consensus of expert opinion after a thorough review primarily of late-breaking clinical trials identified through a broad-based vetting process as important to the relevant patient population, as well as of other new data deemed to have an impact on patient care (see Section 1.1., Evidence Review, for details regarding this focused update). It is important to note that this focused update is not intended to represent an update based on a full literature review from the date of the previous guideline publication. Specific criteria/considerations for inclusion of new data include the following:

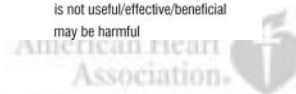
- Publication in a peer-reviewed journal
- Large randomized, placebo-controlled trial(s)
- Nonrandomized data deemed important on the basis of results affecting current safety and efficacy assumptions
- Strength/weakness of research methodology and findings
- Likelihood of additional studies influencing current findings
- Impact on current performance measure(s) and/or likelihood of need to develop new performance measure(s)
- Requests and requirements for review and update from the practice community, key stakeholders, and other sources free of relationships with industry or other potential bias
- Number of previous trials showing consistent results
- Need for consistency with a new guideline or guideline revision

In analyzing the data and developing updated recommendations and supporting text, the focused update writing group used evidence-based methodologies developed by the ACCF/AHA Task Force on Practice Guidelines, which are described elsewhere.¹

The schema for class of recommendation and level of evidence is summarized in Table 1, which also illustrates how the grading system provides an estimate of the size of the treatment effect and an estimate of the certainty of the treatment effect. Note that a recommendation with Level of Evidence B or C does not imply that the recommendation is weak. Many important clinical questions addressed in guidelines do not lend themselves to clinical trials. Although randomized trials may not be available, there may be a very clear clinical consensus that a particular test or therapy is

Table 1. Applying Classification of Recommendations and Level of Evidence

		SIZE OF TREATMENT EFFECT →			
		CLASS I <i>Benefit >>> Risk</i> Procedure/Treatment SHOULD be performed/administered	CLASS IIa <i>Benefit >> Risk</i> <i>Additional studies with focused objectives needed</i> IT IS REASONABLE to perform procedure/administer treatment	CLASS IIb <i>Benefit ≥ Risk</i> <i>Additional studies with broad objectives needed; additional registry data would be helpful</i> Procedure/Treatment MAY BE CONSIDERED	CLASS III <i>Risk ≥ Benefit</i> Procedure/Treatment should NOT be performed/administered SINCE IT IS NOT HELPFUL AND MAY BE HARMFUL
ESTIMATE OF CERTAINTY (PRECISION) OF TREATMENT EFFECT	LEVEL A Multiple populations evaluated* Data derived from multiple randomized clinical trials or meta-analyses	<ul style="list-style-type: none"> Recommendation that procedure or treatment is useful/effective Sufficient evidence from multiple randomized trials or meta-analyses 	<ul style="list-style-type: none"> Recommendation in favor of treatment or procedure being useful/effective Some conflicting evidence from multiple randomized trials or meta-analyses 	<ul style="list-style-type: none"> Recommendation's usefulness/efficacy less well established Greater conflicting evidence from multiple randomized trials or meta-analyses 	<ul style="list-style-type: none"> Recommendation that procedure or treatment is not useful/effective and may be harmful Sufficient evidence from multiple randomized trials or meta-analyses
	LEVEL B Limited populations evaluated* Data derived from a single randomized trial or nonrandomized studies	<ul style="list-style-type: none"> Recommendation that procedure or treatment is useful/effective Evidence from single randomized trial or nonrandomized studies 	<ul style="list-style-type: none"> Recommendation in favor of treatment or procedure being useful/effective Some conflicting evidence from single randomized trial or nonrandomized studies 	<ul style="list-style-type: none"> Recommendation's usefulness/efficacy less well established Greater conflicting evidence from single randomized trial or nonrandomized studies 	<ul style="list-style-type: none"> Recommendation that procedure or treatment is not useful/effective and may be harmful Evidence from single randomized trial or nonrandomized studies
	LEVEL C Very limited populations evaluated* Only consensus opinion of experts, case studies, or standard of care	<ul style="list-style-type: none"> Recommendation that procedure or treatment is useful/effective Only expert opinion, case studies, or standard of care 	<ul style="list-style-type: none"> Recommendation in favor of treatment or procedure being useful/effective Only diverging expert opinion, case studies, or standard of care 	<ul style="list-style-type: none"> Recommendation's usefulness/efficacy less well established Only diverging expert opinion, case studies, or standard of care 	<ul style="list-style-type: none"> Recommendation that procedure or treatment is not useful/effective and may be harmful Only expert opinion, case studies, or standard of care
Suggested phrases for writing recommendations†		should is recommended is indicated is useful/effective/beneficial	is reasonable can be useful/effective/beneficial is probably recommended or indicated	may/might be considered may/might be reasonable usefulness/effectiveness is unknown/unclear/uncertain or not well established	is not recommended is not indicated should not is not useful/effective/beneficial may be harmful



*Data available from clinical trials or registries about the usefulness/efficacy in different 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 ACC/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.



useful and effective. Both the class of recommendation and level of evidence listed in the focused updates are based on consideration of the evidence reviewed in previous iterations of the guideline as well as the focused update. Of note, the implications of older studies that have informed recommendations but have not been repeated in contemporary settings are carefully considered.

The ACCF/AHA practice guidelines address patient populations (and healthcare providers) residing in North America. As such, drugs that are not currently available in North America are discussed in the text without a specific class of recommendation. For studies performed in large numbers of subjects outside of North America, each writing committee reviews the potential impact of different practice patterns and patient populations on the treatment effect and on the relevance to the ACCF/AHA target population to determine whether the findings should inform a specific recommendation.

The ACCF/AHA practice guidelines are intended to assist healthcare providers in clinical decision making by describing a range of generally acceptable approaches for the diagnosis, management, and prevention of specific diseases or conditions. The guidelines attempt to define practices that meet the needs of most patients in most circumstances. The ultimate judgment regarding care of a particular patient must be made by the healthcare provider and patient in light of all the circumstances presented by that patient. Thus, there are circumstances in which deviations from these guidelines may be appropriate. Clinical decision making should consider the quality and availability of expertise in the area where care is provided. These guidelines may be used as the basis for regulatory or payer decisions, but the ultimate goals are quality of care and serving the patient's best interests.

Prescribed courses of treatment in accordance with these recommendations are effective only if they are followed by the patient. Because lack of patient adherence may adversely

affect treatment outcomes, healthcare providers should make every effort to engage the patient in active participation with prescribed treatment.

The ACCF/AHA Task Force on Practice Guidelines makes every effort to avoid actual, potential, or perceived conflict of interest that may arise as a result of industry relationships or personal interests among the writing committee. Specifically, all members of the writing committee, as well as peer reviewers of the document, are asked to disclose all such relationships pertaining to the trials and other evidence under consideration (see Appendixes 1 and 2). Final recommendations were balloted to all writing committee members. Writing committee members with significant (greater than \$10 000) relevant relationships with industry were required to recuse themselves from voting on that recommendation. Writing committee members who did not participate are not listed as authors of this focused update.

With the exception of the recommendations presented here, the full guideline remains current. Only the recommendations from the affected section(s) of the full guideline are included in this focused update. For easy reference, all recommendations from any section of a guideline affected by a change are presented with notation as to whether they remain current, are new, or have been modified. When evidence affects recommendations in more than 1 set of guidelines, those guidelines are updated concurrently.

The recommendations in this focused update are considered current until they are superseded by another focused update or the full-text guidelines are revised. This focused update is published in the April 14, 2009, issues of the *Journal of the American College of Cardiology* and *Circulation* as an update to the full-text guideline and is also posted on the ACCF (www.acc.org, www.cardiosource.com) and AHA (my.americanheart.org) Web sites. A revised version of the ACC/AHA 2005 Guideline Update for the Diagnosis and Management of Chronic Heart Failure in the Adult² full-text guideline that incorporates the focused update has also been e-published in these issues and is available on the respective Web sites.³ For easy reference, that online-only version denotes sections that have been updated.

Sidney C. Smith, Jr, MD, FACC, FAHA
Chair, ACCF/AHA Task Force on Practice Guidelines

Alice K. Jacobs, MD, FACC, FAHA
Vice-Chair, ACCF/AHA Task Force on Practice Guidelines

1. Introduction

1.1. Evidence Review

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, were reviewed by the standing guideline writing committee along with the parent task force and other experts 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 ACC/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 heart failure (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 already been made public. Thus, the committee thought that a new section about this important aspect of HF care should be added to this update.

When considering the new data for this 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.

Policy on clinical areas not covered by the present focused update can be found in the 2009 Focused Update Incorporated into the ACC/AHA 2005 Guidelines for the Diagnosis and Management of Heart Failure in Adults.³

1.2. Organization of Committee and Relationships With Industry

For this 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 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

This document was reviewed by 2 external reviewers nominated by the ACCF and 2 external reviewers nominated by the 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 2 for details).

This document 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.

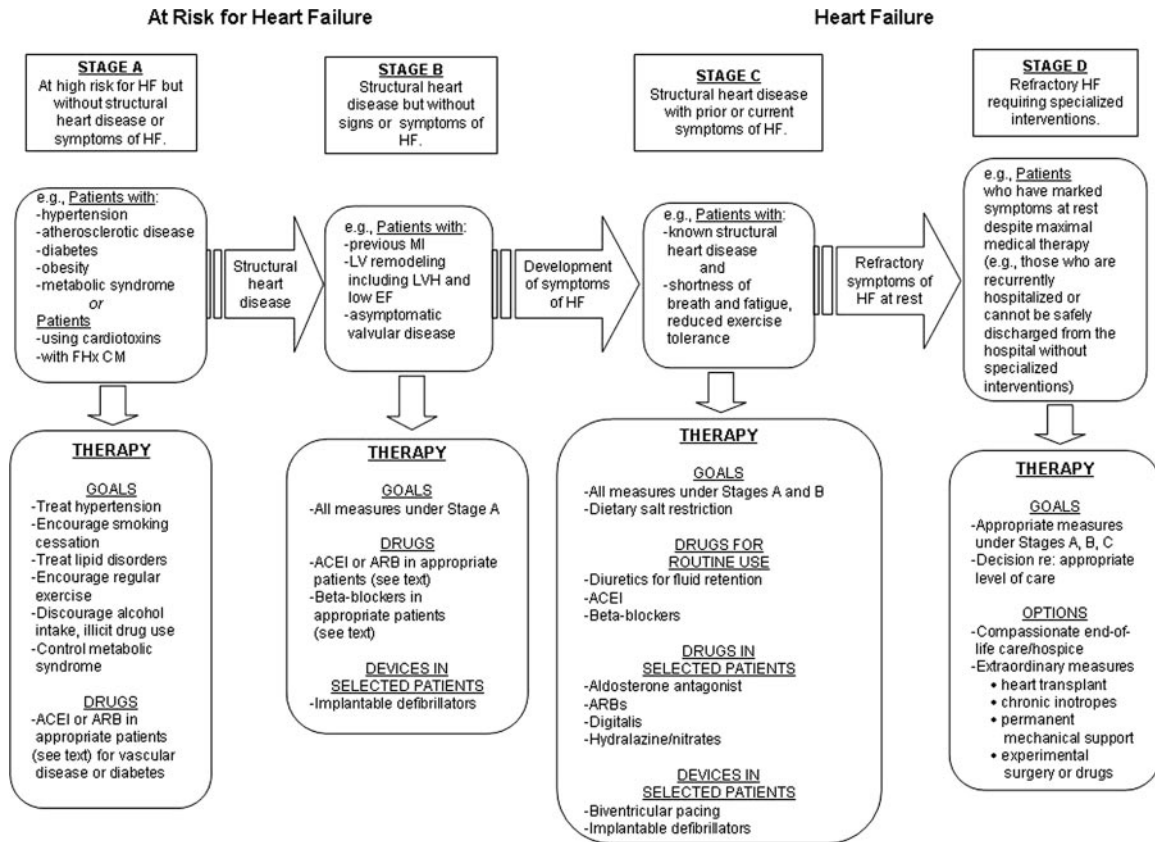


Figure 1. Stages in the Development of Heart Failure/Recommended Therapy by Stage. ACEI indicates angiotensin-converting enzyme inhibitors; ARB, angiotensin II receptor blocker; EF, ejection fraction; FHx CM, family history of cardiomyopathy; HF, heart failure; LVH, left ventricular hypertrophy; and MI, myocardial infarction.

1.4. Stages of Heart Failure: Information From the 2005 Guideline

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 (Figure 1). 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 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.

3. Initial and Serial Clinical Assessment of Patients Presenting With Heart Failure

The changes in this section are made to clarify the role of functional assessment of the HF patient, beyond the New York Heart Association (NYHA) 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).

3.1. Initial Evaluation of Patients

3.1.1. Identification of Patients

In general, patients with LV dysfunction or HF present to the healthcare provider in 1 of 3 ways:

- 1. With a syndrome of decreased exercise tolerance.** Most patients with HF seek medical attention with complaints of a reduction in their effort tolerance due to dyspnea and/or fatigue. These symptoms, which may occur at rest or during exercise, may be attributed inappropriately by the patient and/or healthcare provider to aging, other physiological abnormalities (e.g., deconditioning), or other medical disorders (e.g., pulmonary disease). Therefore, in a patient whose exercise capacity is limited by dyspnea or fatigue, the healthcare provider must determine whether the principal cause is HF or another abnormality. Elucidation of the precise reason for exercise intolerance can be

Table 2. Updates to Section 3. Initial and Serial Clinical Assessment of Patients Presenting With Heart Failure

2005 Guideline Recommendations	2009 Focused Update Recommendations	Comments
3. Recommendations for the Initial Clinical Assessment of Patients Presenting With Heart Failure		
Class I		
A thorough history and physical examination should be obtained/performed in patients presenting with HF to identify cardiac and noncardiac disorders or behaviors that might cause or accelerate the development or progression of HF. (<i>Level of Evidence: C</i>)	1. A thorough history and physical examination should be obtained/performed in patients presenting with HF to identify cardiac and noncardiac disorders or behaviors that might cause or accelerate the development or progression of HF. (<i>Level of Evidence: C</i>)	2005 recommendation remains current in the 2009 update.
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. (<i>Level of Evidence: C</i>)	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. (<i>Level of Evidence: C</i>)	2005 recommendation remains current in the 2009 update.
In patients presenting with HF, initial assessment should be made of the patient's ability to perform routine and desired activities of daily living. (<i>Level of Evidence: C</i>)	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. (<i>Level of Evidence: C</i>)	2005 recommendation remains current in the 2009 update.
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. (<i>Level of Evidence: C</i>)	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. (<i>Level of Evidence: C</i>)	2005 recommendation remains current in the 2009 update.
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. (<i>Level of Evidence: C</i>)	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. (<i>Level of Evidence: C</i>)	2005 recommendation remains current in the 2009 update.
Twelve-lead electrocardiogram and chest radiograph (posterior to anterior [PA] and lateral) should be performed initially in all patients presenting with HF. (<i>Level of Evidence: C</i>)	6. Twelve-lead electrocardiogram and chest radiograph (PA and lateral) should be performed initially in all patients presenting with HF. (<i>Level of Evidence: C</i>)	2005 recommendation remains current in the 2009 update.
Two-dimensional echocardiography with Doppler should be performed during initial evaluation of patients presenting with HF to assess left ventricular ejection fraction (LVEF), LV size, wall thickness, and valve function. Radionuclide ventriculography can be performed to assess LVEF and volumes. (<i>Level of Evidence: C</i>)	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. (<i>Level of Evidence: C</i>)	2005 recommendation remains current in the 2009 update.
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. (<i>Level of Evidence: B</i>)	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. ⁴⁻⁸ (<i>Level of Evidence: B</i>)	2005 recommendation remains current in the 2009 update.
Class IIa		
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. (<i>Level of Evidence: C</i>)	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. (<i>Level of Evidence: C</i>)	2005 recommendation remains current in the 2009 update.
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. (<i>Level of Evidence: C</i>)	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. (<i>Level of Evidence: C</i>)	2005 recommendation remains current in the 2009 update.
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. (<i>Level of Evidence: B</i>)	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. ⁹ (<i>Level of Evidence: B</i>)	2005 recommendation remains current in the 2009 update.

(continued)

Table 2. Continued

2005 Guideline Recommendations	2009 Focused Update Recommendations	Comments
	Class IIa (Continued)	
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)	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)	2005 recommendation remains current in the 2009 update.
Maximal exercise testing with measurement of respiratory gas exchange is reasonable to identify high-risk patients presenting with HF who are candidates for cardiac transplantation or other advanced treatments. (Level of Evidence: B)	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. ¹⁰⁻¹² (Level of Evidence: B)	2005 recommendation remains current in the 2009 update.
Screening for hemochromatosis, sleep-disturbed breathing, or human immunodeficiency virus is reasonable in selected patients who present with HF. (Level of Evidence: C)	6. Screening for hemochromatosis, sleep-disturbed breathing, or human immunodeficiency virus is reasonable in selected patients who present with HF. (Level of Evidence: C)	2005 recommendation remains current in the 2009 update.
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)	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)	2005 recommendation remains current in the 2009 update.
Endomyocardial biopsy can be useful in patients presenting with HF when a specific diagnosis is suspected that would influence therapy. (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. ¹³ (Level of Evidence: C)	2005 recommendation remains current in the 2009 update.
Measurement of BNP can be useful in the evaluation of patients presenting in the urgent care setting in whom the clinical diagnosis of HF is uncertain. (Level of Evidence: A)	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 useful in risk stratification. ¹⁴⁻²¹ (Level of Evidence: A)	Modified recommendation (added a caveat on natriuretic peptides and their role as part of total evaluation, in both diastolic and systolic dysfunction).
	Class IIb	
Noninvasive imaging may be considered to define the likelihood of coronary artery disease in patients with HF and LV dysfunction. (Level of Evidence: C)	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)	2005 recommendation remains current in the 2009 update.
Holter monitoring might be considered in patients presenting with HF who have a history of myocardial infarction (MI) and are being considered for electrophysiologic study to document ventricular tachycardia (VT) inducibility. (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)	2005 recommendation remains current in the 2009 update.
	Class III	
Endomyocardial biopsy should not be performed in the routine evaluation of patients with HF. (Level of Evidence: C)	1. Endomyocardial biopsy should not be performed in the routine evaluation of patients with HF. ¹³ (Level of Evidence: C)	2005 recommendation remains current in the 2009 update.
Routine use of signal-averaged electrocardiography is not recommended for the evaluation of patients presenting with HF. (Level of Evidence: C)	2. Routine use of signal-averaged electrocardiography is not recommended for the evaluation of patients presenting with HF. (Level of Evidence: C)	2005 recommendation remains current in the 2009 update.
Routine measurement of circulating levels of neurohormones (e.g., norepinephrine or endothelin) is not recommended for 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)	2005 recommendation remains current in the 2009 update.
3. Recommendations for Serial Clinical Assessment of Patients Presenting With Heart Failure		
	Class I	
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)	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)	2005 recommendation remains current in the 2009 update.

(continued)

Table 2. Continued

2005 Guideline Recommendations	2009 Focused Update Recommendations	Comments
	Class I (Continued)	
Assessment should be made at each visit of the volume status and weight of a patient with HF. (<i>Level of Evidence: C</i>)	2. Assessment should be made at each visit of the volume status and weight of a patient with HF. (<i>Level of Evidence: C</i>)	2005 recommendation remains current in the 2009 update.
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. (<i>Level of Evidence: C</i>)	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. (<i>Level of Evidence: C</i>)	2005 recommendation remains current in the 2009 update.
	Class IIa	
Repeat measurement of ejection fraction (EF) and the severity of structural remodeling can provide useful information in patients with HF who have had a change in clinical status or who have experienced or recovered from a clinical event or received treatment that might have had a significant effect on cardiac function. (<i>Level of Evidence: C</i>)	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. (<i>Level of Evidence: C</i>)	2005 recommendation remains current in the 2009 update.
	Class IIb	
The value of serial measurements of BNP to guide therapy for patients with HF is not well established. (<i>Level of Evidence: C</i>)	1. The value of serial measurements of BNP to guide therapy for patients with HF is not well established. (<i>Level of Evidence: C</i>)	2005 recommendation remains current in the 2009 update.

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).²²

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,²³ 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

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.²⁴ 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.²⁵

Magnetic resonance imaging may also be used to identify myocardial viability and scar tissue.²⁶ 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.

3.1.3.2. Laboratory Testing

Laboratory testing may reveal the presence of disorders or conditions that can lead to or exacerbate HF. The initial evaluation of patients with HF should include a complete blood 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 mea-

sured, 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,¹³ and Section 3.1.3.4, Evaluation of the Possibility of Myocardial Disease, in the full-text guideline. 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 emigrated 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,²⁷ 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.²⁸ Elevated levels lend support to a diagnosis of abnormal ventricular function or hemodynamics causing symptomatic HF.²⁹ 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,⁴ and suggest that its use may reduce both the time to hospital discharge and the cost of treatment.³⁰ BNP levels tend to be less elevated in HF with preserved EF than in HF with low EF and are lower in obese patients.^{31,32} 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 non-cardiac 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.^{30,33}

3.2.3. Laboratory Assessment

Serum electrolytes and renal function should be monitored routinely in patients with HF. Of particular importance is the

serial measurement of serum potassium concentration, because hypokalemia is a common adverse effect of treatment with diuretics and may cause fatal arrhythmias and increase the risk of digitalis toxicity, whereas hyperkalemia may complicate therapy with angiotensin-converting enzyme (ACE) inhibitors, angiotensin 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 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. in the full-text guideline, Laboratory Testing).²⁹ 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.³⁴ 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.³⁵

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

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.³⁶ 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.^{36,37} 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,³⁸ 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.³⁸ 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.³⁹

4. Therapy

4.3.1. Patients With Reduced Left Ventricular Ejection Fraction

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.^{39,40} 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).

4.3.1.1. General Measures

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.^{142–145}

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

1. Antiarrhythmic agents¹⁴⁶ can exert important cardiodepressant and proarrhythmic effects. Of available agents, only amiodarone and dofetilide¹⁴⁷ 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.¹⁴⁸ Of available calcium channel blockers, only the vasoselective ones have been shown not to adversely affect survival.^{139,149}
3. Nonsteroidal anti-inflammatory drugs can cause sodium retention and peripheral vasoconstriction and can attenuate the efficacy and enhance the toxicity of diuretics and ACE inhibitors.^{84–87} 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, in the full-text guideline).

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.¹⁵⁰ Activation of both the sympathetic nervous system and renin-angiotensin system can lead to hypokalemia,^{151,152} and most drugs used for the treatment of HF can alter serum potassium.¹⁵³ Even modest decreases in serum potassium can increase the risks of using digitalis and antiarrhythmic drugs,^{150,154} and even modest increases in serum potassium may prevent the use of treatments known to prolong life.¹⁵⁵ Hence, many experts believe that serum potassium concentrations should be targeted in the 4.0 to 5.0 mmol per liter range. In some patients, correction of potassium deficits may require supplementation of magnesium and potassium.¹⁵⁶ In others (particularly those taking ACE inhibitors 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.^{157–160}

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.^{155,161} 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

Table 3. Updates to Section 4.3.1. Patients With Reduced Left Ventricular Ejection Fraction

2005 Guideline Recommendations	2009 Focused Update Recommendations	Comments
4.3.1. Patients With Reduced Left Ventricular Ejection Fraction		
Class I		
Measures listed as Class I recommendations for patients in stages A and B are also appropriate for patients in Stage C. (<i>Levels of Evidence: A, B, and C as appropriate</i>)	1. Measures listed as Class I recommendations for patients in stages A and B are also appropriate for patients in Stage C. (<i>Levels of Evidence: A, B, and C as appropriate</i>)	2005 recommendation remains current in 2009 update.
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). (<i>Level of Evidence: C</i>)	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 in the full-text guidelines). (<i>Level of Evidence: C</i>)	2005 recommendation remains current in 2009 update.
Angiotensin converting enzyme inhibitors are recommended for all patients with current or prior symptoms of HF and reduced LVEF, unless contraindicated (see text, Table 3 in the full-text guidelines). (<i>Level of Evidence: A</i>)	3. Angiotensin-converting enzyme inhibitors are recommended for all patients with current or prior symptoms of HF and reduced LVEF, unless contraindicated (see text, Table 3 in the full-text guidelines). ^{41–53} (<i>Level of Evidence: A</i>)	2005 recommendation remains current in 2009 update.
Beta blockers (using 1 of the 3 proven to reduce mortality, i.e., bisoprolol, carvedilol, and sustained release metoprolol succinate) are recommended for all stable patients with current or prior symptoms of HF and reduced LVEF, unless contraindicated (see text, Table 3 in the full-text guidelines). (<i>Level of Evidence: A</i>)	4. Beta blockers (using 1 of the 3 proven to reduce mortality, i.e., bisoprolol, carvedilol, and sustained release metoprolol succinate) are recommended for all stable patients with current or prior symptoms of HF and reduced LVEF, unless contraindicated (see text, Table 3 in the full-text guidelines). ^{54–72} (<i>Level of Evidence: A</i>)	2005 recommendation remains current in 2009 update.
Angiotensin II receptor blockers approved for the treatment of HF (see Table 3) are recommended in patients with current or prior symptoms of HF and reduced LVEF who are ACE inhibitor-intolerant (see text for information regarding patients with angioedema). (<i>Level of Evidence: A</i>)	5. Angiotensin II receptor blockers (see Table 3 in the full-text guidelines) are recommended in patients with current or prior symptoms of HF and reduced LVEF who are ACE inhibitor-intolerant (see text for information regarding patients with angioedema). ^{73–83} (<i>Level of Evidence: A</i>)	2005 recommendation remains current but text modified to eliminate specific agents tested.
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). (<i>Level of Evidence: B</i>)	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). ^{84–90} (<i>Level of Evidence: B</i>)	2005 recommendation remains current in 2009 update.
Maximal exercise testing with or without measurement of respiratory gas exchange is recommended to facilitate prescription of an appropriate exercise program for patients with HF. (<i>Level of Evidence: C</i>)		2005 recommendation no longer current. See 2009 Class IIa No. 2 recommendation below.
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. (<i>Level of Evidence: B</i>)	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. ^{90a–90d} (<i>Level of Evidence: B</i>)	2005 recommendation remains current in 2009 update.
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. (<i>Level of Evidence: A</i>)	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. ^{91–93} (<i>Level of Evidence: A</i>)	2005 recommendation remains current in 2009 update.
Implantable cardioverter-defibrillator therapy is recommended for primary prevention to reduce total mortality by a reduction in sudden cardiac death in patients with ischemic heart disease who are at least 40 days post-MI, have an LVEF less than or equal to 30%, with NYHA functional class II or III symptoms while undergoing chronic optimal medical therapy, and have reasonable expectation of survival with a good functional status for more than 1 year. (<i>Level of Evidence: A</i>)	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. ^{40,93–99} (<i>Level of Evidence: A</i>)	Modified recommendation to be consistent with the ACC/AHA/Heart Rhythm Society (HRS) 2008 Device-Based Therapy guidelines.

(continued)

Table 3. Continued

2005 Guideline Recommendations	2009 Focused Update Recommendations Class I (Continued)	Comments
Implantable cardioverter-defibrillator therapy is recommended for primary prevention to reduce total mortality by a reduction in sudden cardiac death in patients with nonischemic cardiomyopathy who have an LVEF less than or equal to 30%, with NYHA functional class II or III symptoms while undergoing chronic optimal medical therapy, and who have reasonable expectation of survival with a good functional status for more than 1 year. (Level of Evidence: B)	2005 recommendation no longer current. See 2009 Class I No. 9 recommendation above.	
Patients with LVEF less than or equal to 35%, sinus rhythm, and NYHA functional class III or ambulatory class IV symptoms despite recommended, optimal medical therapy and who have cardiac dyssynchrony, which is currently defined as a QRS duration greater than 120 ms, should receive cardiac resynchronization therapy unless contraindicated. (Level of Evidence: A)	10. Patients with LVEF of less than or equal to 35%, sinus rhythm, and NYHA functional class III or ambulatory class IV symptoms despite recommended, optimal medical therapy and who have cardiac dyssynchrony, which is currently defined as a QRS duration greater than or equal to 0.12 seconds, should receive cardiac resynchronization therapy, with or without an ICD, unless contraindicated. ^{100–115} (Level of Evidence: A)	Clarified recommendation (includes therapy with or without an ICD).
Addition of an aldosterone antagonist is reasonable in selected patients with moderately severe to severe symptoms of HF and reduced LVEF who can be carefully monitored for preserved renal function and normal potassium concentration. Creatinine should be less than or equal to 2.5 mg per dL in men or less than or equal to 2.0 mg per dL 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. (Level of Evidence: B)	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. ^{116–118} (Level of Evidence: B)	2005 recommendation remains current in 2009 update.
	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 ACE inhibitors, beta blockers, and diuretics. ^{119,120} (Level of Evidence: B)	New recommendation
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. ^{121–125} (Level of Evidence: A)	New recommendation
Angiotensin II receptor blockers are reasonable to use as alternatives to ACE inhibitors as first-line therapy for patients with mild to moderate HF and reduced LVEF, especially for patients already taking ARBs for other indications. (Level of Evidence: A)	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)	Modified recommendation (changed class of recommendation from I to IIa).
Digitalis can be beneficial in patients with current or prior symptoms of HF and reduced LVEF to decrease hospitalizations for HF. (Level of Evidence: B)	3. Angiotensin II receptor blockers are reasonable to use as alternatives to ACE inhibitors as first-line therapy for patients with mild to moderate HF and reduced LVEF, especially for patients already taking ARBs for other indications. ^{73–82} (Level of Evidence: A)	2005 recommendation remains current in 2009 update.
The addition of a combination of hydralazine and a nitrate is reasonable for patients with reduced LVEF who are already taking an ACE inhibitor and beta-blocker for symptomatic HF and who have persistent symptoms. (Level of Evidence: B)	4. Digitalis can be beneficial in patients with current or prior symptoms of HF and reduced LVEF to decrease hospitalizations for HF. ^{126–133} (Level of Evidence: B)	2005 recommendation remains current in 2009 update.
Placement of an implantable cardioverter-defibrillator is reasonable in patients with LVEF of 30% to 35% of any origin with NYHA functional class II or III symptoms who are taking chronic optimal medical therapy and who have reasonable expectation of survival with good functional status of more than 1 year. (Level of Evidence: B)	5. The addition of a combination of hydralazine and a nitrate is reasonable for patients with reduced LVEF who are already taking an ACE inhibitor and beta blocker for symptomatic HF and who have persistent symptoms. ^{119,134} (Level of Evidence: B)	2005 recommendation remains current in 2009 update.
		2005 recommendation no longer current. See 2009 Class I No. 9 recommendation above.

(continued)

Table 3. Continued

2005 Guideline Recommendations	2009 Focused Update Recommendations	Comments
	Class IIa (Continued)	
	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. ^{3,135} (Level of Evidence: B)	New recommendation added to be consistent with the ACC/AHA/HRS 2008 Device-Based Therapy guidelines. ⁴⁰
	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. ³ (Level of Evidence: C)	New recommendation added to be consistent with the ACC/AHA/HRS 2008 Device-Based Therapy guidelines.
	Class IIb	
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 ACE inhibitor or ARB because of drug intolerance, hypotension, or renal insufficiency. (Level of Evidence: C)	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 ACE inhibitor or ARB because of drug intolerance, hypotension, or renal insufficiency. ^{119,136,137} (Level of Evidence: C)	2005 recommendation remains current in 2009 update.
The addition of an ARB may be considered in persistently symptomatic patients with reduced LVEF who are already being treated with conventional therapy. (Level of Evidence: B)	2. The addition of an ARB may be considered in persistently symptomatic patients with reduced LVEF who are already being treated with conventional therapy. ^{73–82} (Level of Evidence: B)	2005 recommendation remains current in 2009 update.
	Class III	
Routine combined use of an ACE inhibitor, ARB, and aldosterone antagonist is not recommended for patients with current or prior symptoms of HF and reduced LVEF. (Level of Evidence: C)	1. Routine combined use of an ACE inhibitor, ARB, and aldosterone antagonist is not recommended for patients with current or prior symptoms of HF and reduced LVEF. (Level of Evidence: C)	2005 recommendation remains current in 2009 update.
Calcium channel blocking drugs are not indicated as routine treatment for HF in patients with current or prior symptoms of HF and reduced LVEF. (Level of Evidence: A)	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. ^{138–141} (Level of Evidence: A)	2005 recommendation remains current in 2009 update.
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)	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)	2005 recommendation remains current in 2009 update.
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)	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)	2005 recommendation remains current in 2009 update.
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)	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)	2005 recommendation remains current in 2009 update.

mEq per liter 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 (83) were receiving spironolactone, the safety of the combination of ACE inhibitors, ARBs, and aldosterone antagonists has not been explored adequately, and this combination cannot be recommended.

4.3.1.2.5. *Ventricular Arrhythmias and Prevention of Sudden Death.* Patients with LV dilation and reduced LVEF frequently manifest ventricular tachyarrhythmias, both nonsus-

tained 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,¹⁶² 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.¹⁶³

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.^{54,58,60,164,165} Aldosterone antagonists decrease sudden death and overall mortality in HF early after MI and in advanced HF.¹⁶¹ Sudden unexpected death can be decreased further by the use of implanted devices that terminate sustained arrhythmias.^{40,102} 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.⁹⁵ 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.^{166–168} Antiarrhythmic drugs to suppress premature ventricular depolarizations and nonsustained ventricular arrhythmias have not improved survival,^{88,89} 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.^{90,146,169} 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),^{88,89,170,171} which have increased mortality in post-MI trials.¹⁷² Amiodarone is a class III antiarrhythmic agent but differs from other drugs in this class in having a sympatholytic effect on the heart.¹⁷³ Amiodarone has been associated with overall neutral effects on survival when administered to patients with low EF and HF.^{93,174–176} 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.^{175,176} 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.⁹⁶

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.^{93,97,98} 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.⁹⁷ 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.⁹⁸ 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%.⁹³ 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 class I to III HF, and an LVEF less than 36%.¹⁷⁷ 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)⁹⁷ and the SCD-HeFT (Sudden Cardiac Death in Heart Failure: Trial of prophylactic amiodarone versus implantable defibrillator therapy).⁹²

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.¹⁷⁸

It is important to recognize that ICDs have the potential to aggravate HF and have been associated with an increase in HF hospitalizations.^{97,99} 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 Abnormalities⁴⁰ 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.^{93,97} 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 ACE inhibitors 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.

4.3.1.3.3. Hydralazine and Isosorbide Dinitrate. In a large-scale trial that compared the vasodilator combination with placebo, the use of hydralazine and isosorbide dinitrate reduced mortality but not hospitalizations in patients with HF treated with digoxin and diuretics but not an ACE inhibitor or beta blocker.^{136,137} However, in another large-scale trial that compared the vasodilator combination with an ACE inhibitor, the ACE inhibitor produced more favorable effects on survival,⁵² 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.¹¹⁹ 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 ACE inhibitor and/or a beta blocker was shown to be of significant benefit.¹²⁰ 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 ACE inhibitor and should not be substituted for ACE inhibitors in patients who are tolerating ACE inhibitors without difficulty.

Despite the lack of data with the vasodilator combination in patients who are intolerant of ACE inhibitors, the combined use of hydralazine and isosorbide dinitrate may be considered as a therapeutic option in such patients. However, compliance with this combination has generally been poor because of the large number of tablets required and the high incidence of adverse reactions.^{52,136} For patients with more severe HF symptoms and ACE inhibitor intolerance, the combination of hydralazine and nitrates is used frequently, particularly when ACE inhibitor therapy is limited by hypotension or renal insufficiency. There are, however, no trials addressing the use of isosorbide dinitrate and hydralazine specifically in the population of patients who have persistent symptoms and intolerance to inhibitors of the renin-angiotensin system.

4.3.1.3.4. Cardiac Resynchronization Therapy. Approximately one-third of patients with low EF and Class III to IV symptoms of HF manifest a QRS duration greater than 0.12 seconds.^{179–181} 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.^{182–184} Ventricular dyssynchrony has also been associated with increased mortality in HF patients.^{103–105} 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.^{106–108} 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,¹⁰⁹ as well as adaptive changes in the biochemistry of the failing heart.¹⁰⁷

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 CRT¹¹⁰ or to the combination of CRT and ICD.^{102,111,112} In a meta-analysis of several CRT trials, HF hospitalizations were reduced by 32% and all-cause mortality by 25%.¹¹² The effect on mortality in this meta-analysis became apparent after approximately 3 months of therapy.¹¹² In 1 study, subjects were randomized to optimal pharmacological therapy alone, optimal medical ther-

apy 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%.¹¹³ 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%.¹⁰¹ 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 randomized¹¹⁴ and the other observational,¹¹⁵ 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.⁴⁰

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%.¹¹² 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.¹¹²

4.3.1.5.2. Intermittent Intravenous Positive Inotropic Therapy. Although positive inotropic agents can improve cardiac performance during short- and long-term therapy,^{185,186} long-term oral therapy with these drugs has not improved symptoms or clinical status^{131,187–197} and has been associated with a significant increase in mortality, especially in patients with advanced HF.^{195,198–203} 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.^{204–206}

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.^{204–207} 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,²⁰⁸ 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.^{123,124}

4.4. Patients With Refractory End-Stage Heart Failure (Stage D)

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

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.

Table 4. Updates to Section 4.4. Patients With Refractory End-Stage Heart Failure (Stage D)

2005 Guideline Recommendations	2009 Focused Update Recommendations	Comments
Updates to Section 4.4. Patients With Refractory End-Stage Heart Failure (Stage D)		
Class I		
Meticulous identification and control of fluid retention is recommended in patients with refractory end-stage HF. <i>(Level of Evidence: B)</i>	1. Meticulous identification and control of fluid retention is recommended in patients with refractory end-stage HF. ^{209–216} <i>(Level of Evidence: B)</i>	2005 recommendation remains current in 2009 update.
Referral for cardiac transplantation in potentially eligible patients is recommended for patients with refractory end-stage HF. <i>(Level of Evidence: B)</i>	2. Referral for cardiac transplantation in potentially eligible patients is recommended for patients with refractory end-stage HF. ²¹⁷ <i>(Level of Evidence: B)</i>	2005 recommendation remains current in 2009 update.
Referral of patients with refractory end-stage HF to an HF program with expertise in the management of refractory HF is useful. <i>(Level of Evidence: A)</i>	3. Referral of patients with refractory end-stage HF to a HF program with expertise in the management of refractory HF is useful. ^{218–221} <i>(Level of Evidence: A)</i>	2005 recommendation remains current in 2009 update.
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. <i>(Level of Evidence: C)</i>	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. <i>(Level of Evidence: C)</i>	2005 recommendation remains current in 2009 update.
Patients with refractory end-stage HF and implantable defibrillators should receive information about the option to inactivate defibrillation. <i>(Level of Evidence: C)</i>	5. Patients with refractory end-stage HF and implantable defibrillators should receive information about the option to inactivate the defibrillator. <i>(Level of Evidence: C)</i>	2005 recommendation remains current in 2009 update.
Class IIa		
Consideration of an LV assist device as permanent or “destination” therapy is reasonable in highly selected patients with refractory end-stage HF and an estimated 1-year mortality over 50% with medical therapy. <i>(Level of Evidence: B)</i>	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. ^{222,223} <i>(Level of Evidence: B)</i>	2005 recommendation remains current in 2009 update.
Class IIb		
Pulmonary artery catheter placement may be reasonable to guide therapy in patients with refractory end-stage HF and persistently severe symptoms. <i>(Level of Evidence: C)</i>	1. Pulmonary artery catheter placement may be reasonable to guide therapy in patients with refractory end-stage HF and persistently severe symptoms. ^{217,224} <i>(Level of Evidence: C)</i>	2005 recommendation remains current in 2009 update.
The effectiveness of mitral valve repair or replacement is not established for severe secondary mitral regurgitation in refractory end-stage HF. <i>(Level of Evidence: C)</i>	2. The effectiveness of mitral valve repair or replacement is not well established for severe secondary mitral regurgitation in refractory end-stage HF. ^{225–227} <i>(Level of Evidence: C)</i>	2005 recommendation remains current in 2009 update.
Continuous intravenous infusion of a positive inotropic agent may be considered for palliation of symptoms in patients with refractory end-stage HF. <i>(Level of Evidence: C)</i>	3. Continuous intravenous infusion of a positive inotropic agent may be considered for palliation of symptoms in patients with refractory end-stage HF. ^{228,229} <i>(Level of Evidence: C)</i>	2005 recommendation remains current in 2009 update.
Class III		
Partial left ventriculectomy is not recommended in patients with nonischemic cardiomyopathy and refractory end-stage HF. <i>(Level of Evidence: C)</i>	1. Partial left ventriculectomy is not recommended in patients with nonischemic cardiomyopathy and refractory end-stage HF. <i>(Level of Evidence: C)</i>	2005 recommendation remains current in 2009 update.
Routine intermittent infusions of positive inotropic agents are not recommended for patients with refractory end-stage HF. <i>(Level of Evidence: B)</i>	2. Routine intermittent infusions of vasoactive and positive inotropic agents are not recommended for patients with refractory end-stage HF. ^{230,231} <i>(Level of Evidence: A)</i>	Modified recommendation (changed Level of Evidence from B to A).

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 transplan-

tation, 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, Treatment for Special Populations). When no further therapies are appropriate, careful discussion of the prognosis and options for end-of-life

care should be initiated (see Section 7, End-of-Life Considerations, in the full-text guideline).²

4.4.3. Intravenous Peripheral Vasodilators and Positive Inotropic Agents

Patients with refractory HF are hospitalized frequently for clinical deterioration, and during such admissions, they commonly receive infusions of both positive inotropic agents (dobutamine, dopamine, or milrinone) and vasodilator drugs (nitroglycerin, nitroprusside, or nesiritide) in an effort to improve cardiac performance, facilitate diuresis, and promote clinical stability. Some physicians have advocated the placement of pulmonary artery catheters in patients with refractory HF, with the goal of obtaining hemodynamic measurements that might be used to guide the selection and titration of therapeutic agents.²²⁴ 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.^{232,233} 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.²³⁴

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.^{228,229} 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.²²⁰ 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.^{220,230,231}

4.5. The Hospitalized Patient (New)

New recommendations and text have been developed on the hospitalized patient (Table 5).

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 in the full-text guideline) are just as likely to be admitted to hospital as those with HF and low LVEF.²⁵¹ 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.^{252–256} Indeed, many HF trials now incorporate the need for hospitalization as an important end point 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

Table 5. Recommendations for the Hospitalized Patient

2009 Focused Update Recommendations	Comments
Class I	
<p>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:</p> <ul style="list-style-type: none"> 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. <p>Chest radiographs, electrocardiogram, and echocardiography are key tests in this assessment. <i>(Level of Evidence: C)</i></p>	New recommendation
<p>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.^{235,236} <i>(Level of Evidence: A)</i></p>	New recommendation
<p>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. <i>(Level of Evidence: C)</i></p>	New recommendation
<p>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:</p> <ul style="list-style-type: none"> • acute coronary syndromes/coronary ischemia; • severe hypertension; • atrial and ventricular arrhythmias; • infections; • pulmonary emboli; • renal failure; and • medical or dietary noncompliance. <i>(Level of Evidence: C)</i> 	New recommendation
<p>5. Oxygen therapy should be administered to relieve symptoms related to hypoxemia. <i>(Level of Evidence: C)</i></p>	New recommendation
<p>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. <i>(Level of Evidence: C)</i></p>	New recommendation
<p>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.^{21,237,238} <i>(Level of Evidence: B)</i> 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. <i>(Level of Evidence: C)</i></p>	New recommendation
<p>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. <i>(Level of Evidence: C)</i></p>	New recommendation
<p>9. When diuresis is inadequate to relieve congestion, as evidenced by clinical evaluation, the diuretic regimen should be intensified using either:</p> <ul style="list-style-type: none"> 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. <i>(Level of Evidence: C)</i> 	New recommendation
<p>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. <i>(Level of Evidence: C)</i></p>	New recommendation
<p>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. <i>(Level of Evidence: C)</i></p>	New recommendation
<p>12. Medications should be reconciled in every patient and adjusted as appropriate on admission to and discharge from the hospital. <i>(Level of Evidence: C)</i></p>	New recommendation
<p>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 ACE inhibitors 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. <i>(Level of Evidence: C)</i></p>	New recommendation

(continued)

Table 5. Continued

2009 Focused Update Recommendations		Comments
Class I (Continued)		
14. In patients hospitalized with HF with reduced ejection fraction not treated with oral therapies known to improve outcomes, particularly ACE inhibitors or ARBs and beta-blocker therapy, initiation of these therapies is recommended in stable patients prior to hospital discharge. ^{239,240} (Level of Evidence: B)		New recommendation
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. ^{239,240} (Level of Evidence: B)		New recommendation
16. In all patients hospitalized with HF, both with preserved (see Section 4.3.2., Patients With HF and Normal LVEF, in the full-text guideline) 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, worsening renal function and HF signs/symptoms. (Level of Evidence: C)		New recommendation
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 ACE inhibitor/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)		New recommendation
18. Postdischarge systems of care, if available, should be used to facilitate the transition to effective outpatient care for patients hospitalized with HF. ^{112,241–247} (Level of Evidence: B)		New recommendation
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)		New recommendation
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)		New recommendation
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 <ol style="list-style-type: none"> whose fluid status, perfusion, or systemic or pulmonary vascular resistances are uncertain. whose systolic pressure remains low, or is associated with symptoms, despite initial therapy, whose renal function is worsening with therapy who require parenteral vasoactive agents or who may need consideration for advanced device therapy or transplantation. (Level of Evidence: C) 		New recommendation
4. Ultrafiltration is reasonable for patients with refractory congestion not responding to medical therapy. ²⁴⁸ (Level of Evidence: B)		New recommendation
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)		New recommendation
Class III		
1. Use of parenteral inotropes in normotensive patients with acute decompensated HF without evidence of decreased organ perfusion is not recommended. ²⁴⁹ (Level of Evidence: B)		New recommendation
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. ²⁵⁰ (Level of Evidence: B)		New recommendation

evidence from the few available randomized trials evaluating management strategies in the acute decompensated HF patient,^{248–250,257,258} 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.^{259,260,260a}

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, in the full-text guideline). 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.^{261,262} 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.²⁶³ 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^{264,265} 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.^{239,240} 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 ACE inhibitors, 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 ACE inhibitors 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.^{266,267} 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, in the full-text guideline.) 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, in the full-text guideline). 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.^{209,268–274} 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.²⁷⁵

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).^{209,210,274,276–282} 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.^{213,248,283–285} 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.^{286–288} 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.^{257,289–294} 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 cannot 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.^{249,295–297} 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.^{250,298} 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, in the full-text guideline). 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.²⁹⁹

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 HF and Normal LVEF, in the full-text guideline). Particular caution should be used when initiating beta blockers in patients who have required inotropes during their hospital course or when initiating ACE inhibitors 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, in the full-text guideline). 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.³⁰⁰ 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.³⁰¹ 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 regimen²⁴¹ is associated with improved patient outcomes.^{242,302,303}

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.^{112,243–245} 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-analysis²⁴⁶ 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 study²⁴⁷ 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 US hospitals of a standardized set of 30 “Safe Practices” endorsed by the National Quality Forum,³⁰⁴ which overlap in many ways with the National Patient Safety Goals espoused by The Joint Commission.³⁰⁵ 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.³⁰⁶ Fortunately, most US hospitals today have direct access to palliative care services.³⁰⁷ 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.^{308,309}

5. Treatment of Special Populations

The recommendations for hydralazine/isosorbide dinitrate in a specific population have been clarified in this section and in a previous section,^{120,134} based on a recent multicenter trial (Table 6).

6. Patients With Heart Failure Who Have Concomitant Disorders

6.1.3. Supraventricular Arrhythmias

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.³¹²

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.^{313–315}

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)^{316,317} and cardiac relaxation;^{318,319} 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.³²⁰ 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.^{321,322} 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.^{323,324} 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.^{325,326} Hence, digitalis does not block the excessive exercise-induced tachycardia that may limit the functional capacity of patients with HF.^{325–328} Beta blockers are more effective than digoxin during exercise^{325,327} and are preferred because of their favorable effects on the natural history of HF.^{54,58,60} The combination of digoxin and

Table 6. Updates to Section 5. Treatment of Special Populations

2005 Guideline Recommendation	2009 Focused Update Recommendation	Comments
Updates to Section 5. Treatment of Special Populations		
Class I		
	1. The combination of a fixed-dose of isosorbide dinitrate and hydralazine to a standard medical regimen for HF, including ACE inhibitors 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. ^{120,134} (Level of Evidence: A)	Modified recommendation (Class of recommendation elevated from IIa to I) based on A-HeFT (African American Heart Failure Trial) and robust secondary analyses of the original database and in an extended access study all confirm a substantial benefit realized from the addition of isosorbide dinitrate and hydralazine to evidence-based medical and device therapy for African Americans with HF.
Groups of patients including a) high-risk ethnic minority groups (e.g., blacks), b) groups underrepresented in clinical trials, and c) any groups believed to be underserved should, in the absence of specific evidence to direct otherwise, have clinical screening and therapy in a manner identical to that applied to the broader population. (Level of Evidence: B)	2. 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. ^{310,311} (Level of Evidence: B)	2005 recommendation remains current in 2009 update.
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)	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)	2005 recommendation remains current in 2009 update.
Class IIa		
The addition of isosorbide dinitrate and hydralazine to a standard medical regimen for HF, including ACE inhibitors and beta blockers, is reasonable and can be effective in blacks with NYHA functional class III or IV HF. Others may benefit similarly, but this has not yet been tested. (Level of Evidence: A)		Modified recommendation (Class of recommendation elevated from IIa to I) (see Class I, No. 1 above).



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.^{329,330} If beta-blockers are ineffective or contraindicated in patients with atrial fibrillation and HF, amiodarone may be a useful alternative.³³¹ Atrioventricular nodal ablation may be needed if tachycardia persists despite pharmacological therapy.¹⁶⁹ 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.³³²⁻³³⁴ 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.³²⁴

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.³³⁵ 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.^{123,124,324} Most patients revert to atrial fibrillation within a short time unless they are treated with a Class I or III antiarrhythmic drug.³¹³ 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,^{90,146} which can increase the risk of death.^{88,89,170} 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)^{336,337} and proarrhythmia (dofetilide).¹⁴⁷ 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.

Staff

American College of Cardiology Foundation

John C. Lewin, MD, Chief Executive Officer
 Charlene May, Senior Director, Science and Clinical Policy
 Lisa Bradfield, Associate Director, Clinical Policy and Guidelines
 Mark D. Stewart, MPH, Associate Director, Evidence-Based Medicine
 Sue Keller, BSN, MPH, Senior Specialist, Evidence-Based Medicine
 Allison McDougall, Senior Specialist, Practice Guidelines
 Erin A. Barrett, Senior Specialist, Science and Clinical Policy

American Heart Association

Nancy Brown, Chief Executive Officer
 Gayle R. Whitman, PhD, RN, FAHA, FAAN, Senior Vice President, Office of Science Operations

References

- 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.
- Hunt SA, Abraham WT, Casey DE Jr., 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.
- Jessup M, Abraham WT, Casey DE Jr., et al. 2009 focused update incorporated into the ACC/AHA 2005 guidelines for the diagnosis and management of chronic heart failure in adults with the 2008 focused update incorporated. *J Am Coll Cardiol* 2008;53:e1–90.
- 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.
- 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:e340–437.
- 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.
- 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.
- 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.
- 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.
- 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.
- 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.
- 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.
- 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.
- de Lemos JA, McGuire DK, Drazner MH. B-type natriuretic peptide in cardiovascular disease. *Lancet*. 2003;362:316–22.
- 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.
- 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.
- Bayes-Genis A, Santalo-Bel M, Zapico-Muniz E, et al. N-terminal pro-brain 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.
- 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.
- 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.
- 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.
- 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.
- 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.
- The Criteria Committee of the New York Heart Association. *Diseases of the Heart and Blood Vessels: Nomenclature and Criteria for Diagnosis*. 6th Edition. Boston, MA: Little, Brown, 1964.
- Vitarelli A, Tiukinhoy S, Di Luzio S, et al. The role of echocardiography in the diagnosis and management of heart failure. *Heart Fail Rev*. 2003;8:181–9.
- 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.
- 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.
- 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.
- Weinfeld MS, Chertow GM, Stevenson LW. Aggravated renal dysfunction during intensive therapy for advanced chronic heart failure. *Am Heart J*. 1999;138:285–90.
- Maisel A. B-type natriuretic peptide levels: a potential novel “white count” for congestive heart failure. *J Card Fail*. 2001;7:183–93.
- 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.
- Wang TJ, Larson MG, Levy D, et al. Impact of obesity on plasma natriuretic peptide levels. *Circulation*. 2004;109:594–600.
- 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.

33. 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.
34. 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.
35. Mahdyoon H, Klein R, Eyer W, et al. Radiographic pulmonary congestion in end-stage congestive heart failure. *Am J Cardiol*. 1989;63:625–7.
36. 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.
37. Levy WC, Mozaffarian D, Linker DT, et al. The Seattle Heart Failure Model: prediction of survival in heart failure. *Circulation*. 2006;113:1424–33.
38. 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.
39. 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–e346.
40. 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). *J Am Coll Cardiol*. 2008;51:e1–62.
41. Captopril Multicenter Research Group. A placebo-controlled trial of captopril in refractory chronic congestive heart failure. *J Am Coll Cardiol*. 1983;2:755–63.
42. Garg R, Yusuf S. Overview of randomized trials of angiotensin-converting enzyme inhibitors on mortality and morbidity in patients with heart failure. Collaborative Group on ACE Inhibitor Trials. *JAMA*. 1995;273:1450–6.
43. 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.
44. 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.
45. Cleland JG, Dargie HJ, Hodsman GP, et al. Captopril in heart failure. A double blind controlled trial. *Br Heart J*. 1984;52:530–5.
46. 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.
47. Cowley AJ, Rowley JM, Stainer KL, et al. Captopril therapy for heart failure. A placebo controlled study. *Lancet*. 1982;2:730–2.
48. 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.
49. 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.
50. Erhardt L, MacLean A, Ilgenfritz J, et al. Fosinopril attenuates clinical deterioration and improves exercise tolerance in patients with heart failure. Fosinopril Efficacy/Safety Trial (FEST) Study Group. *Eur Heart J*. 1995;16:1892–9.
51. Effects of enalapril on mortality in severe congestive heart failure. Results of the Cooperative North Scandinavian Enalapril Survival Study (CONSENSUS). The CONSENSUS Trial Study Group. *N Engl J Med*. 1987;316:1429–35.
52. 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.
53. Effect of enalapril on survival in patients with reduced left ventricular ejection fractions and congestive heart failure. The SOLVD Investigators. *N Engl J Med*. 1991;325:293–302.
54. CIBIS-II Investigators and Committee. The Cardiac Insufficiency Bisoprolol Study II (CIBIS-II): a randomised trial. *Lancet*. 1999;353:9–13.
55. Hjalmarson A, Goldstein S, Fagerberg B, et al. 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). MERIT-HF Study Group. *JAMA*. 2000;283:1295–302.
56. Beta-Blocker Evaluation of Survival Trial Investigators. A trial of the beta-blocker bucindolol in patients with advanced chronic heart failure. *N Engl J Med*. 2001;344:1659–67.
57. 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.
58. MERIT-HF Study Group. 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.
59. 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.
60. Packer M, Bristow MR, Cohn JN, et al. The effect of carvedilol on morbidity and mortality in patients with chronic heart failure. U.S. Carvedilol Heart Failure Study Group. *N Engl J Med*. 1996;334:1349–55.
61. 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.
62. 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.
63. 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.
64. 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.
65. 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.
66. 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.
67. 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.
68. Waagstein F, Bristow MR, Swedberg K, et al. Beneficial effects of metoprolol in idiopathic dilated cardiomyopathy. Metoprolol in Dilated Cardiomyopathy (MDC) Trial Study Group. *Lancet*. 1993;342:1441–6.
69. CIBIS Investigators and Committees. Circulation. A randomized trial of beta-blockade in heart failure. The Cardiac Insufficiency Bisoprolol Study (CIBIS). 1994;90:1765–73.
70. 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.
71. Colucci WS, Packer M, Bristow MR, et al. Carvedilol inhibits clinical progression in patients with mild symptoms of heart failure. US Carvedilol Heart Failure Study Group. *Circulation*. 1996;94:2800–6.
72. 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.
73. 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.
74. 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.

75. 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.
76. Crozier I, Ikram H, Awan N, et al. Losartan in heart failure. Hemodynamic effects and tolerability. Losartan Hemodynamic Study Group. *Circulation*. 1995;91:691–7.
77. Riegger GA, Bouzo H, Petr P, et al. Improvement in exercise tolerance and symptoms of congestive heart failure during treatment with candesartan cilexetil. Symptom, Tolerability, Response to Exercise Trial of Candesartan Cilexetil in Heart Failure (STRETCH) Investigators. *Circulation*. 1999;100:2224–30.
78. Sharma D, Buyse M, Pitt B, et al. Meta-analysis of observed mortality data from all-controlled, double-blind, multiple-dose studies of losartan in heart failure. Losartan Heart Failure Mortality Meta-analysis Study Group. *Am J Cardiol*. 2000;85:187–92.
79. McKelvie RS, Yusuf S, Pericak D, et al. Comparison of candesartan, enalapril, and their combination in congestive heart failure: randomized evaluation of strategies for left ventricular dysfunction (RESOLVD) pilot study. The RESOLVD Pilot Study Investigators. *Circulation*. 1999;100:1056–64.
80. 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.
81. 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.
82. 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.
83. 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.
84. 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.
85. Herchelz 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.
86. 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.
87. 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.
88. 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.
89. 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.
90. 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.
- 90a. 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.
- 90b. 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.
- 90c. 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.
- 90d. 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.
91. 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.
92. 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.
93. 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.
94. 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.
95. 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.
96. Klein HU, Reek S. The MUSTT study: evaluating testing and treatment. *J Interv Card Electrophysiol*. 2000;4 Suppl 1:45–50.
97. 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.
98. 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.
99. 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.
100. 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.
101. 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.
102. 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.
103. 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.
104. 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.
105. Unverferth DV, Magorien RD, Moeschberger ML, et al. Factors influencing the one-year mortality of dilated cardiomyopathy. *Am J Cardiol*. 1984;54:147–52.
106. 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.
107. 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.
108. Toussaint JF, Lavergne T, Ollitrait J, et al. Biventricular pacing in severe heart failure patients reverses electromechanical dyssynchronization from apex to base. *Pacing Clin Electrophysiol*. 2000;23:1731–4.
109. 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.
110. Abraham WT, Fisher WG, Smith AL, et al. Cardiac resynchronization in chronic heart failure. *N Engl J Med*. 2002;346:1845–53.
111. 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.
112. 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.
113. 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.
114. 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.
115. 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.

116. Juurlink DN, Mamdani M, Kopp A, et al. Drug-drug interactions among elderly patients hospitalized for drug toxicity. *JAMA*. 2003;289:1652–8.
117. 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.
118. 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.
119. Carson P, Ziesche S, Johnson G, et al. Racial differences in response to therapy for heart failure: analysis of the vasodilator-heart failure trials. Vasodilator-Heart Failure Trial Study Group. *J Card Fail*. 1999;5:178–87.
120. 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.
121. Stevenson WG, Tedrow U. Management of atrial fibrillation in patients with heart failure. *Heart Rhythm*. 2007;4:S28–S30.
122. Heist EK, Ruskin JN. Atrial fibrillation and congestive heart failure: risk factors, mechanisms, and treatment. *Prog Cardiovasc Dis*. 2006;48:256–69.
123. 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.
124. 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.
125. Van Gelder IC, 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.
126. The effect of digoxin on mortality and morbidity in patients with heart failure. The Digitalis Investigation Group. *N Engl J Med*. 1997;336:525–33.
127. Comparative effects of therapy with captopril and digoxin in patients with mild to moderate heart failure. The Captopril-Digoxin Multicenter Research Group. *JAMA*. 1988;259:539–44.
128. 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.
129. 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.
130. Guyatt GH, Sullivan MJ, Fallen EL, et al. A controlled trial of digoxin in congestive heart failure. *Am J Cardiol*. 1988;61:371–5.
131. DiBianco R, Shabetai R, Kostuk W, et al. A comparison of oral millrinone, digoxin, and their combination in the treatment of patients with chronic heart failure. *N Engl J Med*. 1989;320:677–83.
132. Uretsky BF, Young JB, Shahidi FE, et al. Randomized study assessing the effect of digoxin withdrawal in patients with mild to moderate chronic congestive heart failure: results of the PROVED trial. PROVED Investigative Group. *J Am Coll Cardiol*. 1993;22:955–62.
133. Packer M, Gheorghiadu 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.
134. Cohn JN. The Vasodilator-Heart Failure Trials (V-HeFT). Mechanistic data from the VA Cooperative Studies. Introduction. *Circulation*. 1993;87:VII–4.
135. 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.
136. 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.
137. Loeb HS, Johnson G, Henrick A, et al. Effect of enalapril, hydralazine plus isosorbide dinitrate, and prazosin on hospitalization in patients with chronic congestive heart failure. The V-HeFT VA Cooperative Studies Group. *Circulation*. 1993;87:VI78–VI87.
138. The effect of diltiazem on mortality and reinfarction after myocardial infarction. The Multicenter Diltiazem Postinfarction Trial Research Group. *N Engl J Med*. 1988;319:385–92.
139. 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.
140. 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.
141. Packer M, O'Connor CM, Ghali JK, et al. Effect of amlodipine on morbidity and mortality in severe chronic heart failure. Prospective Randomized Amlodipine Survival Evaluation Study Group. *N Engl J Med*. 1996;335:1107–14.
142. 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.
143. 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.
144. 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.
145. 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.
146. Packer M. Hemodynamic consequences of antiarrhythmic drug therapy in patients with chronic heart failure. *J Cardiovasc Electrophysiol*. 1991;2:S240–S247.
147. Torp-Pedersen C, Moller M, Bloch-Thomsen PE, et al. Dofetilide in patients with congestive heart failure and left ventricular dysfunction. Danish Investigations of Arrhythmia and Mortality on Dofetilide Study Group. *N Engl J Med*. 1999;341:857–65.
148. 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.
149. Elkayam U. Calcium channel blockers in heart failure. *Cardiology*. 1998;89 Suppl 1:38–46.
150. 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.
151. Packer M. Adaptive and maladaptive actions of angiotensin II in patients with severe congestive heart failure. *Am J Kidney Dis*. 1987;10:66–73.
152. Reid JL, Whyte KF, Struthers AD. Epinephrine-induced hypokalemia: the role of beta adrenoceptors. *Am J Cardiol*. 1986;57:23F–7F.
153. 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.
154. Schwartz AB. Potassium-related cardiac arrhythmias and their treatment. *Angiology*. 1978;29:194–205.
155. Pitt B, Zannad F, Remme WJ, et al. The effect of spironolactone on morbidity and mortality in patients with severe heart failure. Randomized Aldactone Evaluation Study Investigators. *N Engl J Med*. 1999;341:709–17.
156. Rude RK. Physiology of magnesium metabolism and the important role of magnesium in potassium deficiency. *Am J Cardiol*. 1989;63:31G–4G.
157. 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.
158. 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.
159. 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.
160. Philbin EF. Comprehensive multidisciplinary programs for the management of patients with congestive heart failure. *J Gen Intern Med*. 1999;14:130–5.
161. 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.
162. 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.
163. Luu M, Stevenson WG, Stevenson LW, et al. Diverse mechanisms of unexpected cardiac arrest in advanced heart failure. *Circulation*. 1989;80:1675–80.

164. The Norwegian Multicenter Study Group. Timolol-induced reduction in mortality and reinfarction in patients surviving acute myocardial infarction. *N Engl J Med*. 1981;304:801-7.
165. A randomized trial of propranolol in patients with acute myocardial infarction. I. Mortality results. *JAMA*. 1982;247:1707-14.
166. Packer M. Sudden unexpected death in patients with congestive heart failure: a second frontier. *Circulation*. 1985;72:681-5.
167. Kjekshus J. Arrhythmias and mortality in congestive heart failure. *Am J Cardiol*. 1990;65:421-81.
168. Packer M. Lack of relation between ventricular arrhythmias and sudden death in patients with chronic heart failure. *Circulation*. 1992;85:150-6.
169. 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.
170. Copley 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.
171. Waldo AL, Camm AJ, deRuyter H, et al. Effect of d-sotalol on mortality in patients with left ventricular dysfunction after recent and remote myocardial infarction. The SWORD Investigators. *Survival With Oral d-Sotalol* (published erratum appears in *Lancet* 1996;348:416). *Lancet*. 1996;348:7-12.
172. 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.
173. Du XJ, Esler MD, Dart AM. Sympatholytic action of intravenous amiodarone in the rat heart. *Circulation*. 1995;91:462-70.
174. Doval HC, Nul DR, Grancelli HO, et al. Randomised trial of low-dose amiodarone in severe congestive heart failure. Grupo de Estudio de la Sobrevida en la Insuficiencia Cardiaca en Argentina (GESICA). *Lancet*. 1994;344:493-8.
175. 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.
176. Massie BM, Fisher SG, Radford M, et al. Effect of amiodarone on clinical status and left ventricular function in patients with congestive heart failure. CHF-STAT Investigators (published erratum appears in *Circulation* 1996 Nov 15;94:2668). *Circulation*. 1996;93:2128-34.
177. 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.
178. 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.
179. 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.
180. 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.
181. 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.
182. 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.
183. 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.
184. Takeshita A, Basta LL, Kioschos JM. Effect of intermittent left bundle branch block on left ventricular performance. *Am J Med*. 1974;56:251-5.
185. 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.
186. 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.
187. 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.
188. Colucci WS, Sonnenblick EH, Adams KF, et al. Efficacy of phosphodiesterase inhibition with milrinone in combination with converting enzyme inhibitors in patients with heart failure. The Milrinone Multicenter Trials Investigators. *J Am Coll Cardiol*. 1993;22:113A-8A.
189. 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.
190. 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.
191. Goldberg AD, Nicklas J, Goldstein S. Effectiveness of imazodan for treatment of chronic congestive heart failure. The Imazodan Research Group. *Am J Cardiol*. 1991;68:631-6.
192. 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.
193. Narahara KA. Oral enoximone therapy in chronic heart failure: a placebo-controlled randomized trial. The Western Enoximone Study Group. *Am Heart J*. 1991;121:1471-9.
194. Roubin GS, Choong CY, Devenish-Mearns 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.
195. Uretsky BF, Jessup M, Konstam MA, et al. Multicenter trial of oral enoximone in patients with moderate to moderately severe congestive heart failure. Lack of benefit compared with placebo. Enoximone Multicenter Trial Group. *Circulation*. 1990;82:774-80.
196. 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 (DIMIT). *J Am Coll Cardiol*. 1993;22:1564-73.
197. 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.
198. Cohn JN, Goldstein SO, Greenberg BH, et al. A dose-dependent increase in mortality with vesnarinone among patients with severe heart failure. Vesnarinone Trial Investigators. *N Engl J Med*. 1998;339:1810-6.
199. Cowley AJ, Skene AM. Treatment of severe heart failure: quantity or quality of life? A trial of enoximone. Enoximone Investigators. *Br Heart J*. 1994;72:226-30.
200. Feldman AM, Bristow MR, Parmley WW, et al. Effects of vesnarinone on morbidity and mortality in patients with heart failure. Vesnarinone Study Group. *N Engl J Med*. 1993;329:149-55.
201. Hampton JR, van Veldhuisen DJ, Kleber FX, et al. Randomised study of effect of ibopamine on survival in patients with advanced severe heart failure. Second Prospective Randomised Study of Ibopamine on Mortality and Efficacy (PRIME II) Investigators. *Lancet*. 1997;349:971-7.
202. 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.
203. Packer M, Carver JR, Rodeheffer RJ, et al. Effect of oral milrinone on mortality in severe chronic heart failure. The PROMISE Study Research Group. *N Engl J Med*. 1991;325:1468-75.
204. 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.
205. Leier CV, Binkley PF. Parenteral inotropic support for advanced congestive heart failure. *Prog Cardiovasc Dis*. 1998;41:207-24.
206. 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.
207. 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.
208. 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.
209. Brater DC, Chennavasin P, Seiwel R. Furosemide in patients with heart failure: shift in dose-response curves. *Clin Pharmacol Ther*. 1980;28:182-6.

210. 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.
211. Cotter G, Weissgarten J, Metzko 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.
212. Faris R, Flather MD, Purcell H, et al. Diuretics for heart failure. *Cochrane Database Syst Rev.* 2006;CD003838.
213. 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.
214. 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.
215. Ciccoira 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.
216. 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.
217. Jessup M, Banner N, Brozyna 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.
218. 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.
219. 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.
220. 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.
221. 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.
222. 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.
223. 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.
224. Connors AF Jr., Speroff T, Dawson NV, et al. The effectiveness of right heart catheterization in the initial care of critically ill patients. *SUPPORT Investigators. JAMA.* 1996;276:889–97.
225. Bolling SF, Pagani FD, Deeb GM, et al. Intermediate-term outcome of mitral reconstruction in cardiomyopathy. *J Thorac Cardiovasc Surg.* 1998;115:381–6.
226. 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.
227. 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.
228. 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.
229. Miller LW, Merkle EJ, Herrmann V. Outpatient dobutamine for end-stage congestive heart failure. *Crit Care Med.* 1990;18:S30–3.
230. 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.
231. 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.
232. 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.
233. 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.
234. Stevenson LW, Massie BM, Francis GS. Optimizing therapy for complex or refractory heart failure: a management algorithm. *Am Heart J.* 1998;135:S293–309.
235. 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.
236. 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.
237. 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:S129–39.
238. 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.
239. 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.
240. 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.
241. 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.
242. 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.
243. 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.
244. 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–e560.
245. Windham BG, Bennett RG, Gottlieb S. Care management interventions for older patients with congestive heart failure. *Am J Manag Care.* 2003;9:447–59.
246. 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.
247. Koelling TM, Johnson ML, Cody RJ, et al. Discharge education improves clinical outcomes in patients with chronic heart failure. *Circulation.* 2005;111:179–85.
248. 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.
249. 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.
250. 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.
251. 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.
252. 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.
253. 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.
254. 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.

255. 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.
256. Haldean 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.
257. Beta-Blocker Heart Attack Trial Research Group. Intravenous nesiritide vs nitroglycerin for treatment of decompensated congestive heart failure: a randomized controlled trial. *JAMA*. 2002;287:1531–40.
258. Konstam MA, Gheorghiadu M, Burnett J Jr., et al. Effects of oral tolvaptan in patients hospitalized for worsening heart failure: the EVEREST Outcome Trial. *JAMA*. 2007;297:1319–31.
259. 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.
260. Adams J, Lindenfeld J, Arnold J, et al. HFSA 2006 comprehensive heart failure practice guideline. *J Card Fail*. 2006;12:e1–119.
- 260a. 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.
261. 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.
262. 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.
263. 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.
264. 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.
265. 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.
266. 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.
267. 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.
268. 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.
269. 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;100:1300.
270. Cody RJ, Covit AB, Schaer GL, et al. Sodium and water balance in chronic congestive heart failure. *J Clin Invest*. 1986;77:1441–52.
271. Vasko MR, Cartwright DB, Knochel JP, et al. Furosemide absorption altered in decompensated congestive heart failure. *Ann Intern Med*. 1985;102:314–8.
272. Shankar SS, Brater DC. Loop diuretics: from the Na-K-2Cl transporter to clinical use. *Am J Physiol Renal Physiol*. 2003;284:F11–21.
273. 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.
274. Cleland JG, Coletta A, Witte K. Practical applications of intravenous diuretic therapy in decompensated heart failure. *Am J Med*. 2006;119:S26–S36.
275. Firth JD, Raine AE, Ledingham JG. Raised venous pressure: a direct cause of renal sodium retention in oedema? *Lancet*. 1988;1:1033–5.
276. 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.
277. Epstein M, Lepp BA, Hoffman DS, et al. Potentiation of furosemide by metolazone in refractory edema. *Curr Ther Res*. 1977;21:656–67.
278. Sica DA, Gehr TW. Diuretic combinations in refractory oedema states: pharmacokinetic-pharmacodynamic relationships. *Clin Pharmacokinet*. 1996;30:229–49.
279. Ellison DH. The physiologic basis of diuretic synergism: its role in treating diuretic resistance. *Ann Intern Med*. 1991;114:886–94.
280. 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.
281. 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.
282. 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.
283. Bourge RC, Tallaj JA. Ultrafiltration: a new approach toward mechanical diuresis in heart failure. *J Am Coll Cardiol*. 2005;46:2052–3.
284. 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.
285. 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.
286. 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.
287. Fung HL, Bauer JA. Mechanisms of nitrate tolerance. *Cardiovasc Drugs Ther*. 1994;8:489–99.
288. 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.
289. Colucci WS, Elkayam U, Horton DP, et al. Intravenous nesiritide, a natriuretic peptide, in the treatment of decompensated congestive heart failure. Nesiritide Study Group. *N Engl J Med*. 2000;343:246–53.
290. 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.
291. 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.
292. 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.
293. 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.
294. 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.
295. 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.
296. 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.
297. 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.

298. 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.
299. 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.
300. 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.
301. 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.
302. Krumholz HM, Baker DW, Ashton CM, et al. Evaluating quality of care for patients with heart failure. *Circulation*. 2000;101:E122–40.
303. 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.
304. 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.
305. The Joint Commission 2008 National Patient Safety Goals. Available at: http://www.jointcommission.org/PatientSafety/NationalPatientSafetyGoals/08_hap_npsgs.htm. Accessed March 1, 2008.
306. 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.
307. 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.
308. 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.
309. 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.
310. 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.
311. Yancy CW. The prevention of heart failure in minority communities and discrepancies in health care delivery systems. *Med Clin North Am*. 2004;88:1347–xiii.
312. 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.
313. Stevenson WG, Stevenson LW. Atrial fibrillation in heart failure (editorial comment). *N Engl J Med*. 1999;341:910–1.
314. 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.
315. 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.
316. 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.
317. Kass DA. Force-frequency relation in patients with left ventricular hypertrophy and failure. *Basic Res Cardiol*. 1998;93 Suppl 1:108–16.
318. 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.
319. 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.
320. 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.
321. 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.
322. 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.
323. 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.
324. Shivkumar K, Jafri SM, Gheorghide 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.
325. 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.
326. 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.
327. 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.
328. 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.
329. Goldstein RE, Boccuzzi SJ, Cruess D, et al. Diltiazem increases late-onset congestive heart failure in postinfarction patients with early reduction in ejection fraction. The Adverse Experience Committee; and the Multicenter Diltiazem Postinfarction Research Group. *Circulation*. 1991;83:52–60.
330. Mohindra SK, Udeani GO. Long-acting verapamil and heart failure (letter). *JAMA*. 1989;261:994.
331. Deedwania PC, Singh BN, Ellenbogen K, et al. 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). The Department of Veterans Affairs CHF-STAT Investigators. *Circulation*. 1998;98:2574–9.
332. 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.
333. 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.
334. 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.
335. Boos CJ, Carlsson J, More RS. Rate or rhythm control in persistent atrial fibrillation? *QJM*. 2003;96:881–92.
336. 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.
337. 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.

KEY WORDS: ACCF/AHA practice guideline ■ focused update ■ heart failure ■ hospitalized patient ■ refractory end-stage heart failure

Appendix 1. 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 (<i>Chair</i>)	<ul style="list-style-type: none"> • Acorn • CardioMEMS • GlaxoSmithKline • Medtronic • Scios • Ventracor 	None	None	None	None	None
Dr. William T. Abraham	<ul style="list-style-type: none"> • Arrow International • AstraZeneca • BioEnergy • Boehringer Ingelheim • CardioKine • CardioKinetix • CardioMEMS* • CHF Solutions • Department of Veterans Affairs Cooperative Studies Program • Edwards Lifesciences • Inovise • Medtronic* • Merck & Co. • National Institutes of Health • Novartis • Paracor • Pfizer • ResMed • Respirationics • Scios • St. Jude Medical* • Sunshine Heart 	<ul style="list-style-type: none"> • Amgen • AstraZeneca • Boehringer Ingelheim • CHF Solutions • GlaxoSmithKline • Guidant Corp. • Medtronic* • Merck & Co. • Novartis • Pfizer • ResMed • Respirationics • Scios Inc. • St. Jude Medical* 	None	<ul style="list-style-type: none"> • Heart Failure Society of America • Medtronic Inc.* • National Institutes of Health • Paracor Inc.* • St. Jude Medical* 	None	None
Dr. Donald E. Casey	None	None	None	None	None	None
Dr. Arthur M. Feldman	<ul style="list-style-type: none"> • Alinea Pharmaceutical • Arca Discovery 	None	<ul style="list-style-type: none"> • CardioKine* 	None	<ul style="list-style-type: none"> • CardioKine* 	None
Dr. Gary S. Francis	<ul style="list-style-type: none"> • Biosite • Boehringer Ingelheim • GlaxoSmithKline • Medtronic • NitroMed • Otsuka 	None	None	None	None	None
Dr. Theodore G. Ganiats	None	None	None	None	None	None
Dr. Marvin A. Konstam	<ul style="list-style-type: none"> • AstraZeneca • CardioKine • GlaxoSmithKline • Merck* • Nitromed • Novartis* • Otsuka* • Sanofi 	<ul style="list-style-type: none"> • Otsuka* 	<ul style="list-style-type: none"> • Orqis* 	<ul style="list-style-type: none"> • GlaxoSmithKline • Nitromed • Otsuka* 	None	None



Circulation

JOURNAL OF THE AMERICAN HEART ASSOCIATION

(continued)

Appendix 1. Continued

Committee Member	Consultant	Speaker	Ownership/ Partnership/ Principal	Research	Institutional, Organizational, or Other Financial Benefit	Expert Witness
Dr. Donna M. Mancini	<ul style="list-style-type: none"> • Acorn • Celladon 	None	None	None	None	None
Dr. Peter S. Rahko	<ul style="list-style-type: none"> • Breast Cancer International Research Group 	<ul style="list-style-type: none"> • Boehringer Ingelheim • GlaxoSmithKline • Novartis 	None	<ul style="list-style-type: none"> • Enoxsive Pharmaceuticals 	None	<ul style="list-style-type: none"> • Deposition, Plaintiff, Myocardial Infarction Post Motor Vehicle Accident
Dr. Marc A. Silver	None	<ul style="list-style-type: none"> • GlaxoSmithKline • Johnson & Johnson 	None	None	None	None
Dr. Lynne Warner Stevenson	None	None	None	<ul style="list-style-type: none"> • CardioMEMS • Medtronic 	None	<ul style="list-style-type: none"> • CardioMEMS • Medtronic
Dr. Clyde W. Yancy	<ul style="list-style-type: none"> • Arc Discovery* • GlaxoSmithKline* • Nitromed • Scios, Inc. 	<ul style="list-style-type: none"> • GlaxoSmithKline* • Novartis 	None	<ul style="list-style-type: none"> • GlaxoSmithKline • Medtronic • Nitromed • 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 2. 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	<ul style="list-style-type: none"> • AstraZeneca • Bristol-Myers Squibb-Sanofi* • GlaxoSmithKline* • Medtronic* • Merck* • Novartis* • Pfizer* 	<ul style="list-style-type: none"> • AstraZeneca • Bristol-Myers Squibb-Sanofi* • GlaxoSmithKline* • Medtronic* • Merck* • Novartis* • Pfizer* 	None	None	None	None
Dr. G. Harold	Official—American College of Cardiology Board of Trustees	None	None	None	None	None	None

(continued)

Appendix 2. Continued

Peer Reviewer	Representation	Consultant	Speaker	Ownership/ Partnership/ Principal	Research	Institutional, Organizational, or Other Financial Benefit	Expert Witness
Dr. Robert E. Hobbs	Official—American College of Cardiology Board of Governors	None	• Scios*	None	None	None	None
Dr. Michael R. Zile	Official—American Heart Association	<ul style="list-style-type: none"> • Bristol-Myers Squibb-Sanofi • Enoxsive • Medtronic • Novartis • Orqis • Ortho Clinical Diagnostic • Synvista 	None	None	<ul style="list-style-type: none"> • Bristol-Myers Squibb-Sanofi • Enoxsive • Medtronic • Novartis • Orqis • Ortho Clinical Diagnostic • 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	<ul style="list-style-type: none"> • Amgen • Boston Scientific • Corthera • Cytokinetics • Geron • XDS 	<ul style="list-style-type: none"> • Amgen • Cytokinetics • 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

(continued)

Appendix 2. Continued

Peer Reviewer	Representation	Consultant	Speaker	Ownership/ Partnership/ Principal	Research	Institutional, Organizational, or Other Financial Benefit	Expert Witness
Dr. Alan B. Miller	Organizational—Heart Failure Society of America	None	<ul style="list-style-type: none"> • AstraZeneca • Bristol-Myers Squibb • CV Therapeutics • GlaxoSmithKline • Novartis 	<ul style="list-style-type: none"> • CV Therapeutics • Medtronic • Merck 	None	None	None
Dr. Srinivas Murali	Organizational—International Society of Heart and Lung Transplantation	None	None	None	<ul style="list-style-type: none"> • Jarvik Inc. • Novacardiac • Paracor Inc. • Scios • Thoratic Inc. • Ventrocor Inc. 	<ul style="list-style-type: none"> • Boston Scientific* (salary) • Medtronic* (salary) • St. Jude Medical* (salary) 	None
Dr. Nancy M. Albert	Content—American Heart Association Heart Failure and Transplant Committee	<ul style="list-style-type: none"> • Arco Biopharma • GlaxoSmithKline • Medtronic 	<ul style="list-style-type: none"> • GlaxoSmithKline 	None	<ul style="list-style-type: none"> • GlaxoSmithKline* • Medtronic* 	None	None
Dr. John D. Bisognano	Content—American College of Cardiology Board of Governors	None	None	None	None	None	None
Dr. Javed Butler	Content—American College of Cardiology Heart Failure and Transplant Committee	None	<ul style="list-style-type: none"> • Boehringer Ingelheim* • GlaxoSmithKline* • Novartis* 	None	None	None	None
Dr. David E. Lanfear	Content—American College of Cardiology Heart Failure and Transplant Committee	<ul style="list-style-type: none"> • Thoratec 	None	None	<ul style="list-style-type: none"> • Merck • Sanofi-Aventis 	None	None
Dr. Joann Lindenfeld	Content—American Heart Association Heart Failure and Transplant Committee	<ul style="list-style-type: none"> • Arca • CV Therapeutics* • Medtronic • Sanofi-Aventis • Takeda 	None	None	<ul style="list-style-type: none"> • Merck • 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	<ul style="list-style-type: none"> • GlaxoSmithKline • NitroMed 	<ul style="list-style-type: none"> • GlaxoSmithKline • NitroMed 	None	None	None	None



Appendix 2. Continued

Peer Reviewer	Representation	Consultant	Speaker	Ownership/ Partnership/ Principal	Research	Institutional, Organizational, or Other Financial Benefit	Expert Witness
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. Petrucci	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.