HFSA 2010 Guideline Executive Summary

Executive Summary: HFSA 2010 Comprehensive Heart Failure Practice Guideline

HEART FAILURE SOCIETY OF AMERICA

St. Paul, Minnesota

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ABSTRACT

Heart failure (HF) is a syndrome characterized by high mortality, frequent hospitalization, reduced quality of life, and a complex therapeutic regimen. Knowledge about HF is accumulating so rapidly that individual clinicians may be unable to readily and adequately synthesize new information into effective strategies of care for patients with this syndrome. Trial data, though valuable, often do not give direction for individual patient management. These characteristics make HF an ideal candidate for practice guidelines. The 2010 Heart Failure Society of America comprehensive practice guideline addresses the full range of evaluation, care, and management of patients with HF.

Key Words: Heart failure, practice guidelines.

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Section 1: Development and Implementation of a Comprehensive Heart Failure Practice Guideline

Heart failure (HF) is a syndrome characterized by high mortality, frequent hospitalization, poor quality of life, multiple comorbidities, and a complex therapeutic regimen. Knowledge about HF is accumulating so rapidly that individual clinicians may be unable to readily and adequately synthesize new information into effective principles of care for patients with this syndrome. Trial data, though valuable, often do not give adequate direction for individual patient management.

Given the complex and changing picture of HF and the accumulation of evidence-based HF therapy, it is not possible for the clinician to rely solely on personal experience and observation to guide therapeutic decisions. The situation is exacerbated because HF is now a chronic condition in most patients, meaning that the outcome of therapeutic decisions might not be apparent for several years. The prognosis of individual patients differs considerably, making it difficult to generalize. Treatments might not dramatically improve symptoms of the disease process, yet might provide important reductions or delays in morbid events and deaths. The assessment of specific therapeutic outcomes is complicated by the potential differential impact of various cotherapies.

The complexity of HF, its high prevalence in society, and the availability of many therapeutic options make it an ideal candidate for practice guidelines. Additional assumptions driving the development of HF guidelines are presented in Table 1.1.

The first HF guideline developed by the Heart Failure Society of America (HFSA) had a narrow scope, concentrating on the pharmacologic treatment of chronic, symptomatic left ventricular dysfunction.[1] It did not consider subsets of the clinical syndrome of HF, such as acute decompensated HF and ''diastolic dysfunction,'' or issues such as prevention. The subsequent comprehensive clinical practice guideline published in 2006 addressed a full range of topics including prevention, evaluation, disease management, and pharmacologic and device therapy for patients with HF.[2] The 2010 guideline updates and expands each of these areas and adds a section on the Genetic Evaluation of Cardiomyopathy published separately in 2009.[3] The discussion of end of life management has also been considerably expanded. Appendix A is a comparison of the 2006

Table 1.1. Assumptions Underlying HFSA Practice Guideline

Clinical decisions must be made.
Correct course of action may not be readily apparent.
Multiple non-pharmacologic, pharmacologic, and device therapies are available.
Reasonably valid methods exist to address knowledge base and evaluate medical evidence.
Data beyond randomized clinical trials exist that enhance medical decision making.
Uncertainties remain concerning approaches to treatment after review of totality of medical evidence.
Expert opinion has a role in management decisions when Strength of Evidence A data are not available to guide management.
A consensus of experts remains the best method of management recommendations when Strength of Evidence A data are not available

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and 2010 guideline, summarizing the modifications, additions, and deletions in the guideline recommendations. Appendix B is a list of acronyms (including clinical trials) used in the 2010 guideline.

HFSA Guideline Approach to Medical Evidence

Two considerations are critical in the development of practice guidelines: assessing strength of evidence and determining strength of recommendation. Strength of evidence is determined both by the type of evidence available and the assessment of validity, applicability, and certainty of a specific type of evidence. Following the lead of previous guidelines, strength of evidence in this guideline is heavily dependent on the source or type of evidence used. The HFSA guideline process has used three grades (A, B, or C) to characterize the type of evidence available to support specific recommendations (Table 1.2).

It must be recognized, however, that the evidence supporting recommendations is based largely on population responses that may not always apply to individuals within the population. Therefore, data may support overall benefit of one treatment over another but cannot exclude that some individuals within the population may respond better to the other treatment. Thus, guidelines can best serve as evidence-based recommendations for management, not as mandates for management in every patient. Furthermore, it must be recognized that trial data on which recommendations are based have often been carried out with background therapy not comparable to therapy in current use. Therefore, physician decisions regarding the management of individual patients may not always precisely match the recommendations. A knowledgeable physician who integrates the guidelines with pharmacologic and physiologic insight and knowledge of the individual being treated should provide the best patient management.

Strength of Evidence A. Randomized controlled clinical trials provide what is considered the most valid form of guideline evidence. Some guidelines require at least 2 positive randomized clinical trials before the evidence for a recommendation can be designated level A. The HFSA guideline committee has occasionally accepted a single randomized, controlled, outcome-based clinical trial as sufficient for level A evidence when the single trial is large with a substantial number of endpoints and has consistent and robust outcomes. However, randomized clinical trial data, whether derived from one or multiple trials, have not been taken simply at face value. They have been evaluated for: (1) endpoints studied, (2) level of significance, (3) reproducibility of findings, (4) generalizability of study results, and (5) sample size and number of events on which outcome results are based.

Table 1.2. Relative Weight of Evidence Used to Develop HFSA Practice Guideline

Hierarchy of Types of Evidence	
Level A	Randomized, Controlled, Clinical Trials
	May be assigned based on results of a single trial
Level B	Cohort and Case-Control Studies
	Post hoc, subgroup analysis, and meta-analysis
	Prospective observational studies or registries
Level C	Expert Opinion
	Observational studies-epidemiologic findings
	Safety reporting from large-scale use in practice

Strength of Evidence B. The HFSA guideline process also considers evidence arising from cohort studies or smaller clinical trials with physiologic or surrogate endpoints. This level B evidence is derived from studies that are diverse in design and may be prospective or retrospective in nature. They may involve subgroup analyses of clinical trials or have a case control or propensity design using a matched subset of trial populations. Dose-response studies, when available, may involve all or a portion of the clinical trial population. Evidence generated from these studies has well-recognized, inherent limitations. Nevertheless, their value is enhanced through attention to factors such as pre-specification of hypotheses, biologic rationale, and consistency of findings between studies and across different populations.

Strength of Evidence C. The present HFSA guideline makes extensive use of expert opinion, or C-level evidence. The need to formulate recommendations based on level C evidence is driven primarily by a paucity of scientific evidence in many areas critical to a comprehensive guideline. For example, the diagnostic process and the steps used to evaluate and monitor patients with established HF have not been the subject of clinical studies that formally test the validity of one approach versus another. In areas such as these, recommendations must be based on expert opinion or go unaddressed.

The value of expert opinion as a form of evidence remains disputed. Many contend that expert opinion is a weak form of observational evidence, based on practice experience and subject to biases and limitations. Advocates believe expert opinion represents a complex synthesis of observational insights into disease pathophysiology and the benefits of therapy in broad populations of patients. They stress the value of the interchange of experience and ideas among colleagues, who collectively treat thousands of patients. Through contact with numerous individual health care providers who may discuss patients with them, experts are exposed to rare safety issues and gain insight into the perceptions of practitioners concerning the efficacy of particular treatments across a wide spectrum of HF.

Despite the case that can be made for its value, recommendations based on expert opinion alone have been limited to those circumstances when a definite consensus could be reached across the guideline panel and reviewers.

HFSA Guideline Approach to Strength of Recommendation

Determining Strength. Although level of evidence is important, the strength given to specific recommendations is

critical. The process used to determine the strength of individual recommendations is complex. The goal of guideline development is to achieve the best recommendations for evaluation and management, considering not only efficacy, but the cost, convenience, side effect profile, and safety of various therapeutic approaches. The HFSA guideline committee often determined the strength of a recommendation by the ''totality of evidence,'' which is a synthesis of all types of available data, pro and con, about a particular therapeutic option.

Totality of Evidence. Totality of evidence includes not only results of clinical trials, but also expert opinion and findings from epidemiologic and basic science studies. Agreement among various types of evidence, especially from different methodologies, increases the likelihood that a particular therapy is valuable. Although many equate evidence-based medicine with the results of a few individual clinical trials, the best judgment seems to be derived from a careful analysis of all available trial data combined with integration of results from the basic laboratory and the findings of epidemiologic studies.

Scale of Strength. The HFSA guideline employs the categorization for strength of recommendation outlined in Table 1.3. There are several degrees of favorable recommendations and a single category for therapies felt to be not effective. The phrase ''is recommended'' should be taken to mean that the recommended therapy or management process should be followed as often as possible in individual patients. Exceptions are carefully delineated. ''Should be considered'' means that a majority of patients should receive the intervention, with some discretion involving individual patients. ''May be considered'' means that individualization of therapy is indicated (Table 1.3). When the available evidence is considered to be insufficient or too premature, or consensus fails, issues are labeled unresolved and included as appropriate at the end of the relevant section.

Table 1.3. HFSA System for Classifying the Strength of Recommendations

''Is recommended''	Part of routine care Exceptions to therapy should be minimized
''Should be considered''	Majority of patients should receive the intervention Some discretion in application to individual patients should be allowed
''May be considered''	Individualization of therapy is indicated
''Is not recommended''	Therapeutic intervention should not be used

Process of Guideline Development

Key steps in the development of this guideline are listed in Table 1.4. Having determined the broad scope of the current guideline, subcommittees of the guideline committee were formed for each section of the guideline. A literature search with relevant key words and phrases for each guideline section were provided to members of the subcommittees and the full Guideline Committee. Members of each subcommittee were asked to review the search and identify any additional relevant medical evidence for each assigned section. Changes in recommendation and background were carried out by each subcommittee with conference calls directed by the Guideline Committee chair. Each section was presented for comments and consensus approval to the Guideline Committee. Once subsections were complete, the Executive Council reviewed and commented on each section and these comments were returned to the Guideline Committee for changes and once complete, for final approval by the Executive Council.

Table 1.4. Steps in the Development of the 2010 HFSA Practice Guideline

Determine the scope of the practice guideline
Form subcommittees with expertise for each guideline section
Perform literature search relevant to each guideline section and distribute to subcommittee and committee members
Solicit additional relevant information from subcommittee and committee members for each subsection
Formulate new recommendations and revise previous recommendations assigning Strength of Recommendation and Strength of Evidence
Form consensus of subcommittee for each section by conference call
Assign writing of additional or revised background by subcommittee
Full committee review of each section with revisions by subcommittee
Review of each completed section by Executive Council with revisions made by full committee and returned to Executive Council for final approval.
Disseminate document
Update document as changes are necessary

Consensus. The development of a guideline involves the selection of individuals with expertise and experience to drive the process of formulating specific recommendations and producing a written document. The role of these experts goes well beyond the formulation of recommendations supported by expert opinion.

Experts involved in the guideline process must function as a collective, not as isolated individuals. Expert opinion is not always unanimous. Interpretations of data vary. Disagreements arise over the generalizability and applicability of trial results to various patient subgroups. Experts are influenced by their own experiences with particular therapies, but still generally agree on the clinical value of trial data. Discomfort with the results of trials reported as positive or negative generally focus on factors that potentially compromise the evidence. Unfortunately, there are no absolute rules for downgrading or upgrading trial results or for deciding that the limitations of the trial are sufficient to negate what has been regarded as a traditionally positive or negative statistical result.

The HFSA Guideline Committee sought resolution of difficult cases through consensus building. An open, dynamic discussion meant that no single voice was allowed to dominate. Written documents were essential to this process, because they provided the opportunity for feedback from all members of the group. On occasion, consensus of opinion was sufficient to override positive or negative results of almost any form of evidence. The HFSA process

had a strong commitment to recommendations based on objective evidence rigorously reviewed by a panel of experts.

Issues that caused difficulty for the HFSA guideline process were some of the more important ones faced by the committee, because they mirrored those that are often most challenging to clinicians in day-to-day practice. The foundation of the HFSA guideline process was the belief that the careful judgment of recognized opinion leaders in these controversial areas is more likely to be correct than ad hoc decisions made ''on the spot'' by physicians in practice.

The involvement of many groups in the development of this guideline helped avoid the introduction of bias, which can be personal, practice-based, or based on financial interest. Committee members and reviewers from the Executive Council received no direct financial support from the HFSA or any other source for the development of the guideline. Support was provided by the HFSA administrative staff, but the writing of the document was performed on a volunteer basis primarily by the Committee. Financial relationships that might represent conflicts of interest were collected annually from all members of the Guideline Committee and the Executive Council. Current relationships are shown in Appendix C.

Dissemination and Continuity. The value of a practice guideline is significantly influenced by the scope of its dissemination. The first and second HFSA guidelines were available on the Internet, and thousands of copies were downloaded. The current document will be implemented on the Internet both for file transfer and as a hypertext source of detailed knowledge concerning HF.

An important final consideration is the continuity of the guideline development process. The intent is to create a ''living document'' that will be updated and amended as necessary to ensure continuing relevance. The rapid development of new knowledge in HF from basic and clinical research and the continuing evolution of pharmacologic and device therapy for this condition provides a strong mandate for timely updates. The HFSA intends to undertake targeted reviews and updates in areas where new research has implications for practice. Section 17: The Genetic Evaluation of Cardiomyopathy is an example of this policy.

Summary

Practice guidelines have become a major part of the clinical landscape and seem likely to become more rather than less pervasive. Some may perceive guidelines as another mechanism for process management or as another instrument for cost control. But there is a more patient-centered rationale for their development, especially for a common, potentially debilitating, and often fatal syndrome such as HF. Despite advances in clinical trial methodology and the extensive use of studies to evaluate therapeutics and the care process, essential elements of the management process remain undefined for many clinical problems. HF is no exception. Traditionally, management guidelines were determined on an ad hoc basis by physicians and other health care providers in the field. The development and utilization of practice guidelines has emerged as an alternative strategy. The methodology of guideline development needs improvement, but when these documents are properly conceived and formulated, their importance to patient care seems evident. This HFSA guideline on HF is designed as a ''living document,'' which will continue to serve as a resource for helping patients with HF.

Section 2: Conceptualization and Working Definition of Heart Failure

HF remains a major and growing societal problem despite advances in detection and therapy.[4-7] However, there is no widely accepted characterization and definition of HF, probably because of the complexity of the syndrome. The conceptualization and working definition of HF presented here emerged as these guidelines were developed. They are critical to understanding HF and approaching its treatment appropriately.

Conceptual Background. HF is a syndrome rather than a primary diagnosis. It has many potential etiologies, diverse clinical features, and numerous clinical subsets. Patients may have a variety of primary cardiovascular diseases and never develop cardiac dysfunction, and those in whom cardiac dysfunction is identified through testing may never develop clinical HF. In addition to cardiac dysfunction, other factors, such as vascular stiffness, dyssynchrony, and renal sodium handling, play major roles in the manifestation of the syndrome of HF.

Patients at risk for many cardiovascular diseases are at risk for HF. Early identification and treatment of risk factors is perhaps the most significant step in limiting the public health impact of HF.[8-10] Emphasis on primary and secondary prevention is particularly critical because of the difficulty of successfully treating left ventricular (LV) dysfunction, especially when severe.[8] Current therapeutic advances in the treatment of HF do not make prevention any less important.

Although HF is progressive, current therapy may provide stability and even reversibility. The inexorable progression of HF from LV remodeling and dysfunction is no longer inevitable. Prolonged survival with mild to moderate LV dysfunction is now possible. Therapy with angiotensin-converting enzyme (ACE) inhibitors or angiotensin receptor blockers (ARBs), beta blockers, and cardiac resynchronization therapy (CRT) can lead to slowing or to partial reversal of remodeling.

Because of this prolonged survival, comorbid conditions, such as coronary artery disease (CAD) or renal failure, can progress, complicating treatment. Given this prolonged survival, considerable attention is devoted in this guideline to disease management, the use of multidrug therapy, and the management of patients with HF at the end of life.

Working Definition. Although HF may be caused by a variety of disorders, the following comprehensive

guideline and this working definition focus on HF primarily from the loss or dysfunction of myocardial muscle or interstitium.

> **HF is a syndrome caused by cardiac dysfunction, generally resulting from myocardial muscle dysfunction or loss and characterized by either LV dilation or hypertrophy or both. Whether the dysfunction is primarily systolic or diastolic or mixed, it leads to neurohormonal and circulatory abnormalities, usually resulting in characteristic symptoms such as fluid retention, shortness of breath, and fatigue, especially on exertion. In the absence of appropriate therapeutic intervention, HF is usually progressive at the level of both cardiac function and clinical symptoms. The severity of clinical symptoms may vary substantially during the course of the disease process and may not correlate with changes in underlying cardiac function. Although HF is progressive and often fatal, patients can be stabilized and myocardial dysfunction and remodeling may improve, either spontaneously or as a consequence of therapy. In physiologic terms, HF is a syndrome characterized by either or both pulmonary and systemic venous congestion and/or inadequate peripheral oxygen delivery, at rest or during stress, caused by cardiac dysfunction.**

Additional Definitions

HF is often classified as HF with reduced systolic function versus HF with preserved systolic function. Myocardial remodeling often precedes the clinical syndrome of HF. Additional definitions are provided in Table 2.1.

Table 2.1. Additional HF Definitions

"HF With Reduced Left Ventricular Ejection Fraction (LVEF)" Sometimes: "HF With a Dilated Left Ventricle"	A clinical syndrome characterized by signs and symptoms of HF and reduced LVEF. Most commonly associated with LV chamber dilation.
"HF With Preserved LVEF" Sometimes: "HF With a Nondilated LV"	A clinical syndrome characterized by signs and symptoms of HF with preserved LVEF. Most commonly associated with a nondilated LV chamber. May be the result of valvular disease or other causes (Section 11).
"Myocardial Remodeling"	Pathologic myocardial hypertrophy or dilation in response to increased myocardial stress. These changes are generally accompanied by pathologic changes in the cardiac interstitium. Myocardial remodeling is generally a progressive disorder.

Section 3: Prevention of Ventricular Remodeling, Cardiac Dysfunction, and Heart Failure

HF is an all-too-frequent outcome of hypertension and arterial vascular disease, making it a major public health concern.[11,12] Epidemiologic, clinical, and basic research have identified a number of antecedent conditions that predispose individuals to HF and its predecessors, LV remodeling and dysfunction.[13-21] Recognition that many of these risk factors can be modified and that treating HF is difficult and costly has focused attention on preventive strategies for HF.

Development of both systolic and diastolic dysfunction related to adverse ventricular remodeling may take years to produce significant ill effects.[22-28] Although the precise mechanisms for the transition to symptomatic HF are not clear, many modifiable factors have been identified that predispose or aggravate the remodeling process and the development of cardiac dysfunction. Treatment of systemic hypertension, with or without LV hypertrophy, reduces the development of HF.[8,29-36] Prevention of myocardial infarction (MI) in patients with atherosclerotic cardiovascular disease is a critical intervention, since occurrence of MI confers an 8- to 10-fold increased risk for subsequent HF.[30] Other modifiable risk factors include anemia, diabetes, hyperlipidemia, obesity, valvular abnormalities, alcohol, certain illicit drugs, some cardiotoxic medications, and diet.[37,38]

Recommendations for Patients With Risk Factors for Ventricular Remodeling, Cardiac Dysfunction, and Heart Failure

3.1 A careful and thorough clinical assessment, with appropriate investigation for known or potential risk factors, is recommended in an effort to prevent development of LV remodeling, cardiac dysfunction, and HF. These risk factors include, but are not limited to, hypertension, hyperlipidemia, atherosclerosis, diabetes mellitus, valvular disease, obesity, physical inactivity, excessive alcohol intake, dietary choices, and smoking. (Strength of Evidence = A)

3.2 The recommended goals for the management of specific risk factors for the development of cardiac dysfunction and HF are shown in Table 3.1.

3.3 ACE inhibitors are recommended for prevention of HF in patients at high risk of this syndrome, including those with CAD, peripheral vascular disease, or stroke. Patients with diabetes and another major risk factor or patients with diabetes who smoke or have microalbuminuria are also at high risk and should receive ACE inhibitors. (Strength of Evidence = A)

3.4 Beta blockers are recommended for patients with prior MI to reduce mortality, recurrent MI, and the development of HF. (Strength of Evidence = A)

Table 3.1. Goals for the Management of Risk Factors for the Development of Heart Failure

Risk Factor	Population	Treatment Goal	Strength of Evidence
Hypertension	No diabetes or renal disease	<140/90 mmHg	A
	Diabetes	<130/80 mmHg	A
	Renal insufficiency and >1g/day of proteinuria	127/75	A
	Renal insufficiency and ≤1 g/day of proteinuria	130/85	A
	Everyone with hypertension	Limit sodium to ≤1500 mg/day	A
Diabetes	See American Diabetes Association (ADA) Guideline		
Hyperlipidemia	See National Cholesterol Education Program (NCEP) Guideline		
Physical Inactivity	Everyone	Sustained aerobic activity 20-30 minutes, 3-5 times weekly	B
Obesity	BMI >30	Weight reduction to achieve BMI <30	C
Excessive alcohol intake	Men	Limit alcohol intake to 1-2 drink equivalents per day	C
	Women	1 drink equivalent per day	
	Those with propensity to abuse alcohol or with alcoholic cardiomyopathy	Abstention	
Smoking	Everyone	Cessation	A
Vitamin/mineral deficiency	Everyone	Diet high in K^+/calcium	B
Poor diet	Everyone	4 or more servings of fruit and vegetables per day; One or more servings of breakfast cereal per week	B

Section 4. Evaluation of Patients for Ventricular Dysfunction and Heart Failure

Patients undergoing evaluation for ventricular dysfunction and HF fall into 3 general groups: (1) patients at risk of developing HF, (2) patients suspected of having HF based on signs and symptoms or incidental evidence of abnormal cardiac structure or function, and (3) patients with established symptomatic HF.

Patients at Risk for Heart Failure

Patients identified to be at risk for HF require aggressive management of modifiable risk factors as outlined in Section 3 of this guideline. Patients with risk factors may have undetected abnormalities of cardiac structure or function. In addition to risk factor reduction, these patients require careful assessment for the presence of symptoms of HF and, depending on their underlying risk, may warrant noninvasive evaluation of cardiac structure and function.

Recommendations for Evaluation of Patients at Risk for Heart Failure

4.1 Evaluation for clinical manifestations of HF with a routine history and physical examination is recommended in patients with the medical conditions or test findings listed in Table 4.1. (Strength of Evidence = B)

4.2 Assessment of Cardiac Structure and Function. Echocardiography with Doppler is recommended to determine cardiac structure and function in asymptomatic patients with the disorders or findings listed in Table 4.2. (Strength of Evidence = B)

4.3 Routine determination of plasma B-type natriuretic peptide (BNP) or N-terminal pro-BNP (NT-proBNP) concentration as part of a screening evaluation for structural heart disease in asymptomatic patients is not recommended. (Strength of Evidence = B)

Table 4.1. Indications for Evaluation of Clinical Manifestations of HF

Conditions	Hypertension
	Diabetes
	Obesity
	CAD (eg, after MI, revascularization)
	Peripheral arterial disease or cerebrovascular disease
	Valvular heart disease
	Family history of cardiomyopathy in a first-degree relative
	History of exposure to cardiac toxins
	Sleep-disordered breathing
Test Findings	Sustained arrhythmias
	Abnormal ECG (eg, LVH, left bundle branch block, pathologic Q waves)
	Cardiomegaly on chest X-ray

Table 4.2. Assess Cardiac Structure and Function in Patients with the Following Disorders or Findings

CAD (eg, after MI, revascularization)
Valvular heart disease
Family history of cardiomyopathy in a first-degree relative
Atrial fibrillation or flutter
Electrocardiographic evidence of LVH, left bundle branch block, or pathologic Q waves
Complex ventricular arrhythmia
Cardiomegaly

Patients Suspected of Having HF

The evaluation of patients suspected of having HF focuses on interpretation of signs and symptoms that have

Table 4.3. Symptoms Suggesting the Diagnosis of HF

Symptoms	Dyspnea at rest or on exertion
	Reduction in exercise capacity
	Orthopnea
	Paroxysmal nocturnal dyspnea (PND) or nocturnal cough
	Edema
	Ascites or scrotal edema
Less specific presentations of HF	Early satiety, nausea and vomiting, abdominal discomfort
	Wheezing or cough
	Unexplained fatigue
	Confusion/delirium
	Depression/weakness (especially in the elderly)

led to the consideration of this diagnosis. Careful history and physical examination, combined with evaluation of cardiac structure and function, should be undertaken to determine the cause of symptoms and to evaluate the degree of underlying cardiac pathology.

Recommendations for Evaluation of Patients Suspected of Having HF

4.4 Symptoms Consistent with HF. The symptoms listed in Table 4.3 suggest the diagnosis of HF. It is recommended that each of these symptoms be elicited in all patients in whom the diagnosis of HF is being considered. (Strength of Evidence = B)

4.5 Physical Examination. It is recommended that patients suspected of having HF undergo careful physical examination with determination of vital signs and careful evaluation for signs shown in Table 4.4. (Strength of Evidence = B)

Table 4.4. Signs to Evaluate in Patients Suspected of Having HF

Cardiac Abnormality	Sign
Elevated cardiac filling pressures and fluid overload	Elevated jugular venous pressure
	S3 gallop
	Rales
	Hepatojugular reflux
	Ascites
	Edema
Cardiac enlargement	Laterally displaced or prominent apical impulse
	Murmurs suggesting valvular dysfunction
Reduced cardiac output	Narrow pulse pressure
	Cool extremities
	Tachycardia with pulsus alternans
Arrhythmia	Irregular pulse suggestive of atrial fibrillation or frequent ectopy

4.6 It is recommended that BNP or NT-proBNP levels be assessed in all patients suspected of having HF, especially when the diagnosis is not certain. (Strength of Evidence = A)

4.7 Differential Diagnosis. The differential diagnoses in Table 4.5 should be considered as alternative explanations for signs and symptoms consistent with HF. (Strength of Evidence = B)

Table 4.5. Differential Diagnosis for HF Symptoms and Signs

Myocardial ischemia
Pulmonary disease (pneumonia, asthma, chronic obstructive pulmonary disease, pulmonary embolus, primary pulmonary hypertension)
Sleep-disordered breathing
Obesity
Deconditioning
Malnutrition
Anemia
Hepatic failure
Chronic kidney disease
Hypoalbuminemia
Venous stasis
Depression
Anxiety and hyperventilation syndromes
Hyper or hypo-thyroidism

Patients With Established HF

The evaluation of patients with an established diagnosis of HF is undertaken to identify the etiology, assess symptom nature and severity, determine functional impairment, and establish a prognosis. Follow-up of patients with HF or cardiac dysfunction involves continuing reassessment of symptoms, functional capacity, prognosis, and therapeutic effectiveness.

Recommendations for the Evaluation of Patients With Established HF

4.8 It is recommended that patients with a diagnosis of HF undergo evaluation as outlined in Table 4.6. (Strength of Evidence = C)

4.9 Symptoms. In addition to symptoms characteristic of HF (dyspnea, fatigue, decreased exercise tolerance, fluid retention), evaluation of the following symptoms should be considered in the diagnosis of HF:

- Angina
- Symptoms suggestive of embolic events
- Symptoms suggestive of sleep-disordered breathing

Table 4.6. Initial Evaluation of Patients With a Diagnosis of HF

Assess clinical severity of HF by history and physical examination
Assess cardiac structure and function
Determine the etiology of HF, with particular attention to reversible causes
Evaluate for coronary disease and myocardial ischemia
Evaluate the risk of life-threatening arrhythmia
Identify any exacerbating factors for HF
Identify comorbidities which influence therapy
Identify barriers to adherence

- Symptoms suggestive of arrhythmias, including palpitations
- Symptoms of possible cerebral hypoperfusion, including syncope, presyncope, or lightheadedness (Strength of Evidence = B)

4.10 Functional Capacity/Activity Level. It is recommended that the severity of clinical disease and functional limitation be evaluated and recorded and the ability to perform typical daily activities be determined. This evaluation may be graded by metrics such as New York Heart Association (NYHA) functional class (Table 4.7) (Strength of Evidence = A) or by the 6-minute walk test. (Strength of Evidence = C)

Table 4.7. Criteria for NYHA Functional Classification in Patients With HF

Class I	No limitation of physical activity. Ordinary physical activity does not cause undue fatigue, palpitation, or dyspnea.
Class II	Slight limitation of physical activity. Comfortable at rest, but ordinary physical activity results in fatigue, palpitations, or dyspnea.
Class III	IIIA: Marked limitation of physical activity. Comfortable at rest, but less than ordinary activity causes fatigue, palpitation, or dyspnea. IIIB: Marked limitation of physical activity. Comfortable at rest, but minimal exertion causes fatigue, palpitation, or dyspnea.
Class IV	Unable to carry on any physical activity without discomfort. Symptoms of cardiac insufficiency present at rest. If any physical activity is undertaken, discomfort is increased.

4.11 Volume Status. The degree of volume excess is a key consideration during treatment. It is recommended that it be routinely assessed by determining:

- Presence of paroxysmal nocturnal dyspnea or orthopnea
- Presence of dyspnea on exertion
- Daily weights and vital signs with assessment for orthostatic changes
- Presence and degree of rales, S3 gallop, jugular venous pressure elevation, hepatic enlargement and tenderness, positive hepatojugular reflux, edema, and ascites (Strength of Evidence = B)

4.12 Standard Laboratory Tests. It is recommended that the following laboratory tests be obtained routinely in patients being evaluated for HF: serum electrolytes, blood urea nitrogen, creatinine, glucose, calcium, magnesium, fasting lipid profile (low-density lipoprotein cholesterol, high-density lipoprotein cholesterol, triglycerides), complete blood count, serum albumin, uric acid, liver function tests, urinalysis, and thyroid function. (Strength of Evidence = B)

4.13 Electrocardiogram (ECG). It is recommended that all patients with HF have an ECG performed to:

- Assess cardiac rhythm and conduction (in some cases, using Holter monitoring or event monitors)
- Assess electrical dyssynchrony (wide QRS or bundle branch block), especially when left ventricular ejection fraction (LVEF) $<35\%$
- Detect LV hypertrophy or other chamber enlargement
- Detect evidence of myocardial infarction (MI) or ischemia
- Assess QTc interval, especially with drugs that prolong QT intervals (Strength of Evidence = B)

4.14 Chest X-Ray. It is recommended that all patients with HF have a postero-anterior and lateral chest X-ray examination for determination of heart size, evidence of fluid overload, detection of pulmonary and other diseases, and appropriate placement of implanted cardiac devices. (Strength of Evidence = B)

4.15 Additional Laboratory Tests. It is recommended that patients with no apparent etiology of HF or no specific clinical features suggesting unusual etiologies undergo additional directed blood and laboratory studies to determine the cause of HF. (Strength of Evidence = B)

4.16 Evaluation of myocardial ischemia is recommended in those who develop new-onset LV systolic dysfunction especially in the setting of suspected myocardial ischemia or worsening symptoms with pre-existing CAD. The choice of testing modality should depend on the clinical suspicion and underlying cardiac risk factors. Coronary angiography should be considered when pre-test probability of underlying ischemic cardiomyopathy is high and an invasive coronary intervention may be considered. (See Section 13 for specific clinical situations and Strength of Evidence)

4.17 Exercise testing for functional capacity is not recommended as part of routine evaluation in patients with HF. Specific circumstances in which maximal exercise testing with measurement of expired gases should be considered include (Strength of Evidence = C):

- Assessing disparity between symptomatic limitation and objective indicators of disease severity
- Distinguishing non HF-related causes of functional limitation, specifically cardiac versus pulmonary
- Considering candidacy for cardiac transplantation or mechanical circulatory support
- Determining the prescription for cardiac rehabilitation
- Addressing specific employment capabilities

4.18 Routine endomyocardial biopsy is not recommended in cases of new-onset HF. Endomyocardial biopsy should be considered in patients with rapidly progressive clinical HF or ventricular dysfunction, despite appropriate medical therapy. Endomyocardial

biopsy also should be considered in patients suspected of having myocardial infiltrative processes, such as sarcoidosis or amyloidosis, or in patients with malignant arrhythmias out of proportion to LV dysfunction, where sarcoidosis and giant cell myocarditis are considerations. (Strength of Evidence = C)

4.19 It is recommended that clinical evaluation at each follow-up visit include determination of the elements listed in Table 4.9. (Strength of Evidence = B)

These assessments should include the same symptoms and signs assessed during the initial evaluation. (Strength of Evidence = B)

Table 4.9. Elements to Determine at Follow-Up Visits of HF Patients

Functional capacity and activity level
Changes in body weight
Patient understanding of and compliance with dietary sodium restriction
Patient understanding of and compliance with medical regimen
History of arrhythmia, syncope, presyncope, palpitation or ICD discharge
Adherence and response to therapeutic interventions
The presence or absence of exacerbating factors for HF, including worsening ischemic heart disease, hypertension, and new or worsening valvular disease

4.20 In the absence of deteriorating clinical presentation, repeat measurements of ventricular volume and LVEF should be considered in these limited circumstances:

- When a prophylactic implantable cardioverter defibrillator (ICD) or cardiac resynchronization therapy (CRT) device and defibrillator (CRT-D) placement is being considered in order to determine that LVEF criteria for device placement are still met after medical therapy (Strength of Evidence = B)
- When patients show substantial clinical improvement (for example, in response to beta blocker treatment or following pregnancy in patients with peripartum cardiomyopathy). Such change may denote improved prognosis, although it does not in itself mandate alteration or discontinuation of specific treatments (see Section 7). (Strength of Evidence = C)
- In alcohol and cardiotoxic substance abusers who have discontinued the abused substance. (Strength of Evidence = C)
- In patients receiving cardiotoxic chemotherapy. (Strength of Evidence = B)

Repeat determination of LVEF is usually unnecessary in patients with previously documented LV dilatation and low LVEF who manifest worsening signs or symptoms of HF, unless the information is needed to justify a change in patient management (such as surgery or device implantation). (Strength of Evidence = C)

4.21 It is recommended that reevaluation of electrolytes and renal function occur at least every 6 months in clinically stable patients and more frequently following changes in therapy or with evidence of change in volume status. More frequent assessment of electrolytes and renal function is recommended in patients with severe HF, those receiving high doses of diuretics, those on aldosterone antagonists, and those who are clinically unstable. (Strength of Evidence = C)

See Section 7 for recommendations for patients on an aldosterone receptor antagonist.

Section 5: Management of Asymptomatic Patients With Reduced Left Ventricular Ejection Fraction

LV remodeling and reduced LVEF should be distinguished from the syndrome of clinical HF. When LVEF is reduced (<40%), but there are no signs and symptoms of HF, the condition frequently is referred to as asymptomatic LV dysfunction (ALVD). It is important to distinguish between ALVD and patients categorized as NYHA Class I HF. Although patients with NYHA Class I HF do not currently have HF symptoms, they may have ALVD currently, or they may have clinical systolic HF with symptoms in the past. In contrast, patients with ALVD have no past history of HF symptoms. It is now well recognized that there may be a latency period when the LVEF is reduced before the development of symptomatic HF. Although most attention in the HF literature has centered on patients with symptoms, evidence now indicates that ALVD is more common than previously assumed. The recent realization that therapies aimed at symptomatic HF may improve outcomes in patients with ALVD has increased the importance of recognizing and treating patients with this condition.

The management of patients with ALVD focuses on controlling cardiovascular risk factors and on the prevention or reduction of progressive ventricular remodeling. Exercise, smoking cessation, hypertension control, as well as treatment with ACE inhibitors (or ARBs) and beta blockers, all have a potential role in the treatment of this syndrome.

Recommendations for the Management of Asymptomatic Patients With Reduced LVEF

5.1 It is recommended that all patients with ALVD exercise regularly according to a physician-directed prescription to avoid general deconditioning; to optimize weight, blood pressure, and diabetes control; and to reduce cardiovascular risk. (Strength of Evidence = C)

5.2 Smoking cessation is recommended in all patients including those with ALVD. (Strength of Evidence = B)

5.3 Alcohol abstinence is recommended if there is current or previous history of excessive alcohol intake. (Strength of Evidence = C)

5.4 It is recommended that all patients with ALVD with hypertension achieve optimal blood pressure control. (Strength of Evidence = B)

5.5 ACE inhibitor therapy is recommended for asymptomatic patients with reduced LVEF (<40%). (Strength of Evidence = A)

5.6 ARBs are recommended for asymptomatic patients with reduced LVEF who are intolerant of ACE inhibitors from cough or angioedema. (Strength of Evidence = C)

Routine use of the combination of ACE inhibitors and ARBs for prevention of HF is not recommended in this population. (Strength of Evidence = C)

5.7 Beta blocker therapy should be considered in asymptomatic patients with reduced LVEF. (post-MI, Strength of Evidence = B; non post-MI, Strength of Evidence = C)

Section 6: Nonpharmacologic Management and Health Care Maintenance in Patients With Chronic Heart Failure

Nonpharmacologic management strategies represent an important contribution to HF therapy. They may significantly impact patient stability, functional capacity, mortality, and quality of life. These strategies include diet and nutrition, oxygen supplementation, and management of concomitant conditions such as sleep apnea, insomnia, depression, and sexual dysfunction. Exercise training may also play a role in appropriate patients. Attention should be focused on the appropriate management of routine health maintenance issues.

Recommendations for Diet and Nutrition

6.1 Dietary instruction regarding sodium intake is recommended in all patients with HF. Patients with HF and diabetes, dyslipidemia, or severe obesity should be given specific dietary instructions. (Strength of Evidence = B)

6.2 Dietary sodium restriction (2-3 g daily) is recommended for patients with the clinical syndrome of HF and preserved *or* depressed left ventricular ejection fraction (LVEF). Further restriction (<2 g daily) may be considered in moderate to severe HF. (Strength of Evidence = C)

6.3 Restriction of daily fluid intake to <2 L is recommended in patients with severe hyponatremia (serum sodium <130 mEq/L) and should be considered for all patients demonstrating fluid retention that is difficult to control despite high doses of diuretic and sodium restriction. (Strength of Evidence = C)

6.4 It is recommended that specific attention be paid to nutritional management of patients with advanced HF and unintentional weight loss or muscle wasting (cardiac cachexia). Measurement of nitrogen balance, caloric intake, and prealbumin may be useful in determining appropriate nutritional supplementation. Caloric supplementation is recommended. Anabolic steroids are not recommended for cachexic patients. (Strength of Evidence = C)

6.5 Patients with HF, especially those on diuretic therapy and restricted diets, should be considered for daily multivitamin-mineral supplementation to ensure adequate intake of the recommended daily value of essential nutrients. Evaluation for specific vitamin or nutrient deficiencies is rarely necessary. (Strength of Evidence = C)

6.6 Documentation of the type and dose of naturoceutical products used by patients with HF is recommended. (Strength of Evidence = C)

Naturoceutical use is not recommended for relief of symptomatic HF or for the secondary prevention of cardiovascular events. Patients should be instructed to avoid using natural or synthetic products containing ephedra (ma huang), ephedrine, or its metabolites because of an increased risk of mortality and morbidity. Products should be avoided that may have significant drug interactions with digoxin, vasodilators, beta blockers, antiarrhythmic drugs, and anticoagulants. (Strength of Evidence = B)

Recommendations for Other Therapies

6.7 Continuous positive airway pressure to improve daily functional capacity and quality of life is recommended in patients with HF and obstructive sleep apnea documented by approved methods of polysomnography. (Strength of Evidence = B)

6.8 Supplemental oxygen, either at night or during exertion, is not recommended for patients with HF in the absence of an indication of underlying pulmonary disease. Patients with resting hypoxemia or oxygen desaturation during exercise should be evaluated for residual fluid overload or concomitant pulmonary disease. (Strength of Evidence = B)

6.9 The identification of treatable conditions, such as sleep-disordered breathing, urologic abnormalities, restless leg syndrome, and depression should be considered in patients with HF and chronic insomnia. Pharmacologic aids to sleep induction may be necessary. Agents that do not risk physical dependence are preferred. (Strength of Evidence = C)

Recommendations for Specific Activity and Lifestyle Issues

6.10 It is recommended that screening for endogenous or prolonged reactive depression in patients with HF be conducted following diagnosis and at periodic intervals as clinically indicated. For pharmacologic

treatment, selective serotonin reuptake inhibitors are preferred over tricyclic antidepressants, because the latter have the potential to cause ventricular arrhythmias, but the potential for drug interactions should be considered. (Strength of Evidence = B)

6.11 Nonpharmacologic techniques for stress reduction may be considered as a useful adjunct for reducing anxiety in patients with HF. (Strength of Evidence = C)

6.12 It is recommended that treatment options for sexual dysfunction be discussed openly with both male and female patients with HF. (Strength of Evidence = C)

The use of phosphodiasterase-5 inhibitors such as sildenafil may be considered for use for sexual dysfunction in patients with chronic stable HF. These agents are not recommended in patients taking nitrate preparations. (Strength of Evidence = C)

Recommendations for Routine Health Care Maintenance

6.13 It is recommended that patients with HF be advised to stop smoking and to limit alcohol consumption to ≤2 standard drinks per day in men or ≤1 standard drink per day in women. Patients suspected of having an alcohol-induced cardiomyopathy should be advised to abstain from alcohol consumption. Patients suspected of using illicit drugs should be counseled to discontinue such use. (Strength of Evidence = B)

6.14 Pneumococcal vaccine and annual influenza vaccination are recommended in all patients with HF in the absence of known contraindications. (Strength of Evidence = B)

6.15 Endocarditis prophylaxis is not recommended based on the diagnosis of HF alone. Consistent with the AHA recommendation, 'prophylaxis should be given for only specific cardiac conditions, associated with the highest risk of adverse outcome from endocarditis.'[39] These are: 'prosthetic cardiac valves; previous infective endocarditis; congenital heart disease (CHD)' such as: 'unrepaired cyanotic CHD, including palliative shunts and conduits; completely repaired congenital heart defect with prosthetic material or device, whether placed by surgery or by catheter intervention, during the first six months after the procedure; repaired CHD with residual defects at the site or adjacent to the site of a prosthetic patch or prosthetic device (which inhibit endothelialization); cardiac transplantation recipients who develop cardiac valvulopathy.' (Strength of Evidence = C)

6.16 Nonsteroidal anti-inflammatory drugs, including cyclooxygenase-2 inhibitors, are not recommended in patients with chronic HF. The risk of renal failure and fluid retention is markedly increased in the setting of reduced renal function or ACE-inhibitor therapy. (Strength of Evidence = B)

6.17 It is recommended that patients with new- or recent-onset HF be assessed for employability following a reasonable period of clinical stabilization. An objective assessment of functional exercise capacity is useful in this determination. (Strength of Evidence = B)

6.18 It is recommended that patients with chronic HF who are employed and whose job description is compatible with their prescribed activity level be encouraged to remain employed, even if a temporary reduction in hours worked or task performed is required. Retraining should be considered and supported for patients with a job demanding a level of physical exertion exceeding recommended levels. (Strength of Evidence = B)

Recommendations for Exercise Testing/Exercise Training

6.19 It is recommended that patients with HF undergo exercise testing to determine suitability for exercise training (patient does not develop significant ischemia or arrhythmias).

If deemed safe, exercise training should be considered for patients with HF in order to facilitate understanding of exercise expectations (heart rate ranges and appropriate levels of exercise training), to increase exercise duration and intensity in a supervised setting, and to promote adherence to a general exercise goal of 30 minutes of moderate activity/exercise, 5 days per week with warm up and cool down exercises. (Strength of Evidence = B)

Section 7: Heart Failure in Patients With Reduced Ejection Fraction

There are 3 primary issues that must be considered when treating HF patients with reduced LVEF: (1) improving symptoms and quality of life, (2) slowing the progression or reversing cardiac and peripheral dysfunction, and (3) reducing mortality. General measures, such as salt restriction, weight loss, lipid control, and other nonpharmacologic measures are addressed in Section 6. Pharmacologic approaches to symptom control, including diuretics, vasodilators, intravenous inotropic drugs, anticoagulants, and antiplatelet agents are discussed at the end of this section.

Two classes of agents have become the recommended cornerstone of therapy to delay or halt progression of cardiac dysfunction and improve mortality: ACE inhibitors and beta blockers. Even while these agents are underused in the treatment of HF, new classes of agents have been added that show an impact on mortality, complicating decisions about optimal pharmacologic therapy. These include

Table 7.1. ACE-inhibitor, Angiotensin Receptor Blocker, and Beta-Blocker Therapy in Heart Failure with Low Ejection Fraction

Generic Name	Trade Name	Initial Daily Dose	Target Dose	Mean Dose Achieved in Clinical Trials
ACE-inhibitors				
Captopril	Capoten	6.25 mg tid	50 mg tid	122.7 mg/day[160]
Enalapril	Vasotec	2.5 mg bid	10 mg bid	16.6 mg/day[42]
Fosinopril	Monopril	5-10 mg qd	80 mg qd	n/a
Lisinopril	Zestril, Prinivil	2.5-5 mg qd	20 mg qd	*4.5 mg/day (low dose ATLAS) 33.2 mg/day (high dose ATLAS)[161]
Quinapril	Accupril	5 mg bid	80 mg qd	n/a
Ramipril	Altace	1.25-2.5 mg qd	10 mg qd	n/a
Trandolapril	Mavik	1 mg qd	4 mg qd	n/a
Angiotensin Receptor Blockers				
Candesartan	Atacand	4-8 mg qd	32 mg qd	24 mg/day[162]
Losartan	Cozaar	12.5-25 mg qd	150 mg qd	129 mg/day[163]
Valsartan	Diovan	40 mg bid	160 mg bid	254 mg/day[164]
Beta-blockers				
Bisoprolol	Zebeta	1.25 mg qd	10 mg qd	8.6 mg/day[47]
Carvedilol	Coreg	3.125 mg bid	25 mg bid	37 mg/day[165]
Carvedilol	Coreg CR	10 mg qd	80 mg qd	
Metoprolol succinate CR/XL	Toprol XL	12.5-25 mg qd	200 mg qd	159 mg/day[48]
Aldosterone Antagonists				
Spironolactone	Aldactone	12.5 to 25 mg qd	25 mg qd	26 mg/day[60]
Eplerenone	Inspra	25 mg qd	50 mg qd	42.6 mg/day[61]
Other Vasodilators				
Fixed dose Hydralazine/ Isosorbide dinitrate	BiDil	37.5 mg hydralazine/20 mg isosorbide dinitrate tid	75 mg hydralazine/40 mg isosorbide dinitrate tid	142.5 mg hydralazine/76 mg isosorbide dinitrate/day[166]
Hydralazine	Apresoline	37.5 mg qid	75 mg qid	270 mg/day[167]
Isosorbide dinitrate	Isordil	20 mg qid	40 mg qid	136 mg/day[167]

*No difference in mortality between high and low dose groups, but 12% lower risk of death or hospitalization in high dose group vs. low dose group.

ARBs, aldosterone antagonists, and the combination of hydralazine and an oral nitrate (Table 7.1).

Recommendations for ACE-inhibitors

There is compelling evidence that ACE inhibitors should be used to inhibit the renin-angiotensin-aldosterone system (RAAS) in all HF patients with reduced LVEF, whether or not they are symptomatic (Table 7.1). A number of large clinical trials have demonstrated improvement in morbidity and mortality in HF patients with reduced LVEF, both chronically and post-MI.[40-42]

7.1 ACE inhibitors are recommended for routine administration to symptomatic and asymptomatic patients with LVEF ≤ 40%. (Strength of Evidence = A)

ACE inhibitors should be titrated to doses used in clinical trials, as tolerated during concomitant up-titration of beta blockers. (Strength of Evidence = C)

Recommendations for Alternatives to ACE-inhibitors

ACE inhibitors can have some troublesome side effects, including cough and angioedema, which may limit therapy with these agents. ARBs have been demonstrated to be well tolerated in randomized trials of patients judged to be intolerant of ACE inhibitors.[43,44] Both drugs have similar effects on blood pressure, renal function, and potassium.[43] Thus, patients intolerant of ACE-inhibitors for these reasons may also be intolerant of ARBs, and the combination of hydralazine and oral nitrates should be considered for these patients.

7.2 It is recommended that other therapy be substituted for ACE inhibitors in the following circumstances:

- In patients who cannot tolerate ACE inhibitors due to cough, ARBs are recommended. (Strength of Evidence = A)

  The combination of hydralazine and an oral nitrate may be considered in such patients not tolerating ARB therapy. (Strength of Evidence = C)

- Patients intolerant to ACE inhibitors from hyperkalemia or renal insufficiency are likely to experience the same side effects with ARBs. In these cases, the combination of hydralazine and an oral nitrate should be considered. (Strength of Evidence = C)

7.3 ARBs are recommended for routine administration to symptomatic and asymptomatic patients with an LVEF ≤ 40% who are intolerant to ACE inhibitors for reasons other than hyperkalemia or renal insufficiency. (Strength of Evidence = A)

7.4 ARBs should be considered in patients experiencing angioedema while on ACE inhibitors based on their underlying risk and with recognition that angioedema has been reported infrequently with ARBs. (Strength of Evidence = B)

The combination of hydralazine and oral nitrates may be considered in such patients not tolerating ARB therapy. (Strength of Evidence = C)

Recommendations for Angiotensin Receptor Blockers

Both ACE inhibitors and ARBs inhibit the RAAS, but by different mechanisms. ACE inhibitors block an enzyme responsible for converting angiotensin I to angiotensin II and for degrading various kinins. However, during chronic therapy, angiotensin II levels are not completely suppressed by ACE inhibitors. ARBs block the effects of angiotensin II on the ATI receptor, independent of the source of angiotensin II production. ARBs have been compared to ACE-inhibitors in several clinical trials, in both chronic HF and in post-MI HF populations.

7.5 Individual ARBs may be considered as initial therapy rather than ACE inhibitors for patients with the following conditions:

- HF Post-MI (Strength of Evidence = A)
- Chronic HF and reduced LVEF (Strength of Evidence = B)

Recommendations for Beta Adrenergic Receptor Blockers

Beta blocker therapy, advocated for HF by some investigators since the 1970s, remains a major advance in the treatment of patients with HF and reduced LVEF. Several large-scale clinical trials, involving more than 10,000 patients, have provided unequivocal evidence of important reductions in both mortality and morbidity.[45-51] The marked beneficial effects of beta blockade has been well demonstrated in large-scale clinical trials of symptomatic patients with NYHA class II-IV HF and reduced LVEF using carvedilol, bisoprolol, and metoprolol controlled release/extended release (CR/XL). [47-51] These trials added beta blockade to background therapy that included ACE inhibitors and diuretics in more than 90% of patients. The trial results support benefit from both $beta_1$ selective and nonselective beta blockers, whether ancillary properties are present or not. beta blocking agents with intrinsic sympathomimetic activity are likely to worsen survival and should be avoided in patients with HF.[52] The beta-blockers studied in clinical trials are now established as routine therapy in patients with reduced LVEF. This therapy is well tolerated by a large majority of patients with HF, even those with comorbid conditions like diabetes mellitus,[53,54] chronic obstructive lung disease,[55] and peripheral vascular disease.[56]

7.6 Beta blockers shown to be effective in clinical trials of patients with HF are recommended for patients with an LVEF $\leq$40%. (Strength of Evidence = A)

7.7 The combination of a beta blocker and an ACE inhibitor is recommended as routine therapy for asymptomatic patients with a LVEF $\leq$40%

- Post-MI (Strength of Evidence = B)
- Non Post-MI (Strength of Evidence = C)

7.8 Beta blocker therapy is recommended for patients with a recent decompensation of HF after optimization of volume status and successful discontinuation of intravenous diuretics and vasoactive agents, including inotropic support. Whenever possible, beta blocker therapy should be initiated in the hospital setting at a low dose prior to discharge in stable patients. (Strength of Evidence = B)

7.9 Beta blocker therapy is recommended in the great majority of patients with HF and reduced LVEF, even if there is concomitant diabetes, chronic obstructive lung disease, or peripheral vascular disease. Beta blocker therapy should be used with caution in patients with diabetes with recurrent hypoglycemia, with asthma, or with resting limb ischemia. Considerable caution should be used if beta blockers are initiated in patients with marked bradycardia ($<$55 beats/min) or marked hypotension (systolic blood pressure $<$80 mm Hg). Beta blockers are not recommended in patients with asthma with active bronchospasm. (Strength of Evidence = C)

7.10 It is recommended that beta blockade be initiated at low doses and uptitrated gradually, typically at 2-week intervals in patients with reduced LVEF, and after 3-10 day intervals in patients with reduced LVEF following newly diagnosed MI. (Strength of Evidence = B)

7.11 It is recommended that beta blocker therapy be continued in most patients experiencing a symptomatic exacerbation of HF during chronic maintenance treatment, unless they develop cardiogenic shock, refractory volume overload, or symptomatic bradycardia (Strength of Evidence = C)

A temporary reduction of dose (generally by one-half) in this setting may be considered. Abrupt discontinuation in patients with symptomatic exacerbation should be avoided, unless the situation is life-threatening. (Strength of Evidence = C)

If discontinued or reduced, beta blockers should be reinstated before the patient is discharged. In general, doses should be uptitrated to the previous well-tolerated dose as soon as safely possible (Strength of Evidence = B)

Recommendations for Combination ACE-inhibitor, ARB, and Beta Adrenergic Receptor Blocker Therapy

7.12 The routine administration of an ARB is not recommended in addition to ACE inhibitor and beta blocker therapy in patients with a recent acute MI and reduced LVEF. (Strength of Evidence = A)

7.13 The addition of an ARB should be considered in patients with HF due to reduced LVEF who have persistent symptoms or progressive worsening despite optimized therapy with an ACE inhibitor and beta blocker. (Strength of Evidence = A)

Recommendations for Aldosterone Antagonists

Sustained activation of aldosterone appears to play an important role in the pathophysiology of HF.[57] Although ACE inhibition may transiently decrease aldosterone secretion, there are diverse stimuli other than angiotensin II for the production of this hormone.[58] Studies suggest a rapid return of aldosterone to levels similar to those before ACE inhibition.[59] Aldosterone antagonists have demonstrated efficacy in both severe HF and in post-MI HF.[60,61] Hyperkalemia is a serious adverse effect associated with both non-selective (i.e. spironolactone) and selective (i.e. eplerenone) aldosterone antagonists. In addition to hyperkalemia, gynecomastia or breast pain may be important side effects of spironolactone, but not eplerenone.

7.14 Administration of an aldosterone antagonist is recommended for patients with NYHA class IV (or class III, previously class IV) HF from reduced LVEF (<35%) while receiving standard therapy, including diuretics. (Strength of Evidence = A)

7.15 Administration of an aldosterone antagonist should be considered in patients following an acute MI, with clinical HF signs and symptoms or history of diabetes mellitus, and an LVEF <40%. Patients should be on standard therapy, including an ACE inhibitor (or ARB) and a beta blocker. (Strength of Evidence = A)

7.16 Aldosterone antagonists are not recommended when creatinine is >2.5 mg/dL (or creatinine clearance is <30 ml/min) or serum potassium is >5.0 mmol/L or in conjunction with other potassium-sparing diuretics. (Strength of Evidence = A)

7.17 It is recommended that serum potassium concentration be monitored frequently following initiation or change in an aldosterone antagonist. Monitoring should reflect protocols followed in clinical trials. (Strength of Evidence = A)

7.18 In the absence of persistent hypokalemia (<4.0 mmol/L), supplemental potassium is not recommended in patients taking an aldosterone antagonist. (Strength of Evidence = A)

Recommendations for Oral Nitrates and Hydralazine

The combination of hydralazine and isosorbide dinitrate has shown efficacy in several trials and plays a role in HF therapy as an alternative to ACE-inhibitors. Based on the results of the African American Heart Failure Trial (A-HeFT), it also is part of standard HF therapy in African Americans with HF and reduced LVEF.

7.19 A combination of hydralazine and isosorbide dinitrate is recommended as part of standard therapy in addition to beta blockers and ACE inhibitors for African Americans with HF and reduced LVEF.

- NYHA III or IV HF (Strength of Evidence = A)
- NYHA II HF (Strength of Evidence = B) (See Section 15: Special Populations)

7.20 A combination of hydralazine and isosorbide dinitrate may be considered in non-African-American patients with HF and reduced LVEF who remain symptomatic despite optimized standard therapy. (Strength of Evidence = C)

Recommendations for Optimal Use of Multi-Drug Therapy

Multi-drug therapy is required for optimal management to slow progression and improve outcome in patients with HF and reduced LVEF. An ACE inhibitor plus a beta blocker is standard background therapy. An ARB can be substituted for an ACE inhibitor if clinically indicated. An ARB can be added to an ACE inhibitor in individuals in whom beta blocker is contraindicated or not tolerated. The optimal choice of additional drug therapy to further improve outcome in patients already treated with 2 of these 3 drugs is not firmly established. An aldosterone inhibitor, an ARB (if the patient is already on an ACE inhibitor) and the combination of isosorbide dinitrate and hydralazine have all been shown to exert further benefit in controlled trials, but have not been the subject of comparative trials. The choice among these agents may be influenced by the patient's age, renal function, serum potassium, racial background, and severity of the clinical syndrome. Certain combinations require careful monitoring.

7.21 Additional pharmacologic therapy should be considered in patients with HF and reduced LVEF who have persistent symptoms or progressive worsening despite optimized therapy with an ACE inhibitor and beta blocker. The choice of specific agent will be influenced by clinical considerations, including renal function status, chronic serum potassium concentration, blood pressure, and volume status. The triple combination of an ACE inhibitor, an ARB, and an aldosterone antagonist is not recommended because of the high risk of hyperkalemia. (Strength of Evidence = C)

- Addition of an ARB. (Strength of Evidence = A)
- Addition of an aldosterone antagonist:
  - for severe HF (Strength of Evidence =A)
  - for moderate HF (Strength of Evidence = C)
  - for post-MI HF (Strength of Evidence = A)
- Addition of the combination of hydralazine/isosorbide dinitrate:
  - for African Americans (Strength of Evidence = A)
  - for others (Strength of Evidence = C)

7.22 Additional pharmacological therapy should be considered in patients with HF and reduced LVEF *who are unable to tolerate a beta blocker* and have persistent symptoms or progressive worsening despite optimized therapy with an ACE inhibitor. The choice of specific agent will be influenced by clinical considerations,

including renal function status, chronic serum potassium concentration, blood pressure and volume status. The triple combination of an ACE inhibitor, an ARB, and an aldosterone antagonist is not recommended due to the high risk of hyperkalemia. (Strength of Evidence = C)

- Addition of an ARB. (Strength of Evidence = C)
- Addition of an aldosterone antagonist:
  - for severe HF (Strength of Evidence = C)
  - for moderate HF (Strength of Evidence = C)
- Addition of the combination of hydralazine/isosorbide dinitrate:
  - for African Americans (Strength of Evidence = C)
  - for others (Strength of Evidence = C)

Recommendations for Diuretic Therapy

Loop and distal tubular diuretics are necessary adjuncts in the medical therapy for HF when symptoms are the result of sodium and water retention. Diuretics reduce congestive symptoms and signs and can be titrated as needed to restore euvolemia and to reach an estimated ''dry'' weight goal for the patient. Relief of signs and symptoms must be achieved without causing side effects, particularly symptomatic hypotension or worsening renal function.

7.23 Diuretic therapy is recommended to restore and maintain normal volume status in patients with clinical evidence of fluid overload, generally manifested by congestive symptoms (orthopnea, edema, and shortness of breath), or signs of elevated filling pressures (jugular venous distention, peripheral edema, pulsatile hepatomegaly, and, less commonly, rales). (Strength of Evidence = A) Loop diuretics rather than thiazide-type diuretics are typically necessary to restore normal volume status in patients with HF. (Strength of Evidence = B)

7.24 The initial dose of diuretic may be increased as necessary to relieve congestion. Restoration of normal volume status may require multiple adjustments over many days and occasionally weeks in patients with severe fluid overload evidenced by massive edema or ascites. After a diuretic effect is achieved with short-acting loop diuretics, increasing administration frequency to twice or even 3 times per day will provide more diuresis with less physiologic perturbation than larger single doses. (Strength of Evidence = B)

Oral torsemide may be considered in patients in whom poor absorption of oral medication or erratic diuretic effect may be present, particularly those with right-sided HF and refractory fluid retention despite high doses of other loop diuretics. (Strength of Evidence = C)

Intravenous administration of diuretics may be necessary to relieve congestion. (Strength of Evidence = A)

Diuretic refractoriness may represent patient nonadherence, a direct effect of diuretic use on the kidney, or progression of underlying cardiac dysfunction.

7.25 Addition of chlorothiazides or metolazone, once or twice daily, to loop diuretics should be considered in patients with persistent fluid retention despite high-dose loop diuretic therapy. But chronic daily use, especially of metolazone, should be avoided if possible because of the potential for electrolyte shifts and volume depletion. These drugs may be used periodically (every other day or weekly) to optimize fluid management. Metolazone will generally be more potent and much longer-acting in this setting and in patients with chronic renal insufficiency, so administration should be adjusted accordingly. Volume status and electrolytes must be monitored closely when multiple diuretics are used. (Strength of Evidence = C)

7.26 Careful observation for the development of side effects, including electrolyte abnormalities, symptomatic hypotension, renal dysfunction, or worsening renal function, is recommended in patients treated with diuretics, especially when used at high doses and in combination. Patients should undergo routine laboratory studies and clinical examination as dictated by their clinical response. (Strength of Evidence = B)

7.27 Patients requiring diuretic therapy to treat fluid retention associated with HF generally require chronic treatment, although often at lower doses than those required initially to achieve diuresis. Decreasing or even discontinuing diuretics may be considered in patients experiencing significant improvement in clinical status and cardiac function or in those who successfully restrict dietary sodium intake. These patients may undergo cautious weaning of diuretic dose and frequency with careful observation for recurrent fluid retention. (Strength of Evidence = C)

7.28 It is recommended that patients and caregivers be given education that will enable them to demonstrate understanding of the early signs of fluid retention and the plan for initial therapy. (Strength of Evidence = C)

Selected patients may be educated to adjust daily dose of diuretic in response to weight gain from fluid overload (typically short-term weight gain of 2 to 4 lb). (Strength of Evidence = C) (See Section 6 for more information on this topic)

Recommendations for Digoxin

Data from the Digitalis Investigation Group (DIG) trial and the combined databases of several other large trials provide evidence of digoxin's efficacy.[62-68] Digoxin is a drug that is inexpensive and can be given once daily, and it continues to have a therapeutic role in symptomatic patients with HF from reduced LVEF.

7.29 Digoxin may be considered to improve symptoms in patients with reduced LVEF (LVEF ≤40%) who have signs or symptoms of HF while receiving standard therapy, including ACE inhibitors and beta blockers:
- NYHA class II-III (Strength of Evidence = B)
- NYHA class IV (Strength of Evidence = C)

7.30 It is recommended that the dose of digoxin, which should be based on lean body mass, renal function, and concomitant medications, should be 0.125 mg daily in the majority of patients and the serum digoxin level should be <1.0 ng/mL, generally 0.7-0.9 ng/mL. (Strength of Evidence = B)

7.31 Digoxin should be considered for achieving adequate control of the ventricular response to atrial fibrillation in patients with HF. (Strength of Evidence = B)

7.32 High doses of digoxin (maintenance dose >0.25 mg daily) for the purpose of rate control are not recommended. (Strength of Evidence = C)

Recommendations for Anticoagulation and Antiplatelet Drugs

Patients with HF are recognized to be at increased risk for arterial or venous thromboembolic events. In addition to atrial fibrillation and poor ventricular function, which promote stasis and increase the risk of thrombus formation, patients with HF have other manifestations of hypercoagulability. Evidence of heightened platelet activation, increased plasma and blood viscosity, and increased plasma levels of fibrinopeptide A, beta—thromboglobulin, D-dimer, and von Willebrand factor have been found in many patients.[69-71] Despite a predisposition, estimates regarding the incidence of thromboemboli in patients with HF vary substantially between 1.4% and 4.2% per 100 patient years.[72-74] Although variability in the reported incidence likely results from differences in the populations studied and the methodology used to identify these events, the consensus is that pulmonary and systemic emboli are not common in HF patients in sinus rhythm. Traditionally, discussion of anticoagulation in patients with HF has centered on warfarin. Antiplatelet agents are often used in patients with HF from ischemic heart disease.

7.33 Treatment with warfarin (goal international normalized ratio [INR] 2.0-3.0) is recommended for all patients with HF and chronic or documented paroxysmal, persistent, or long-standing atrial fibrillation (Strength of Evidence = A) or a history of systemic or pulmonary emboli, including stroke or transient ischemic attack (Strength of Evidence = C), unless contraindicated.

7.34 It is recommended that patients with symptomatic or asymptomatic ischemic cardiomyopathy and documented recent large anterior MI or recent MI with documented LV thrombus be treated with warfarin (goal INR 2.0-3.0) for the initial 3 months post-MI (Strength of Evidence = B) unless contraindicated.

Other patients with ischemic or nonischemic cardiomyopathy and LV thrombus should be considered for chronic anticoagulation, depending on the characteristics of the thrombus, such as its size, mobility, and degree of calcification. (Strength of Evidence = C)

7.35 Long-term treatment with an antiplatelet agent, generally aspirin in doses of 75 to 81 mg, is recommended for patients with HF due to ischemic cardiomyopathy, whether or not they are receiving ACE inhibitors. (Strength of Evidence = B)

Warfarin (goal INR 2.0-3.0) and clopidogrel (75 mg) also have prevented vascular events in post-MI patients and may be considered as alternatives to aspirin. (Strength of Evidence = B)

7.36 Routine use of aspirin is not recommended in patients with HF without atherosclerotic vascular disease. (Strength of Evidence = C)

Recommendations for Amiodarone Therapy

Ventricular arrhythmias are common in HF patients, and sudden cardiac death (SCD) continues to account for a significant proportion of the mortality in this syndrome. Many antiarrhythmic drugs have adverse hemodynamic effects sufficient to have negative consequences in patients with HF. Patients with HF are at higher risk for proarrhythmic effects of antiarrhythmic agents. The major role for the use of these agents in HF is to reduce recurrences of symptomatic arrhythmias, usually in patients who have an ICD.[75]

7.37 Antiarrhythmic agents, including amiodarone, are not recommended for the primary prevention of sudden death in patients with HF. (Strength of Evidence = A).

7.38 In patients with HF and an ICD, amiodarone may be considered to reduce the frequency of recurrent symptomatic arrhythmias causing ICD shocks. (Strength of Evidence = C)

7.39 It is recommended that when amiodarone therapy is initiated, the potential for interactions with other drugs be reviewed. The maintenance doses of digoxin, warfarin, and some statins should be reduced when amiodarone is initiated and then carefully monitored. Adjustment in doses of these drugs and laboratory assessment of drug activity or serum concentration after initiation of amiodarone is recommended. (Strength of Evidence = A)

7.40 Routine use of amiodarone therapy for asymptomatic arrhythmias that are not felt to contribute to HF or ventricular dysfunction is not recommended. (Strength of Evidence = B)

7.41 n-3 polyunsaturated fatty acids (PUFA) may be considered to reduce mortality in HF patients with NYHA class II-IV symptoms and reduced LVEF. (Strength of Evidence = B)

Section 8: Disease Management, Advance Directives, and End-of-Life Care in Heart Failure

The majority of HF care is performed at home by the patient and family or caregiver. If these individuals do not know what is required, fail to see its importance, or face barriers to engagement in self-care, they will not participate effectively. For this reason, comprehensive education and counseling are the foundation for all HF management. The goals of education and counseling are to help patients, their families, and caregivers acquire the knowledge, skills, strategies, problem solving abilities, and motivation necessary for adherence to the treatment plan and effective participation in self-care. The inclusion of family members and other caregivers is especially important, because HF patients often suffer from cognitive impairment, functional disabilities, multiple comorbidities and other conditions that limit their ability to fully comprehend, appreciate, or enact what they learn.[76-82]

Recommendations for Education and Counseling

8.1 It is recommended that patients with HF and their family members or caregivers receive individualized education and counseling that emphasizes self-care. This education and counseling should be delivered by providers using a team approach in which nurses with expertise in HF management provide the majority of education and counseling, supplemented by physician input and, when available and needed, input from dietitians, pharmacists, and other health care providers. (Strength of Evidence = B)

Teaching is not sufficient without skill building and specification of critical target behaviors. It is recommended that essential elements of patient education (with associated skills) are utilized to promote self-care with associated skills shown in Table 8.1. (Strength of Evidence = B)

8.2 It is recommended that patients' literacy, cognitive status, psychological state, culture, and access to social and financial resources be taken into account for optimal education and counseling. Because cognitive impairment and depression are common in HF and can seriously interfere with learning, patients should be screened for these. Patients found to be cognitively impaired need additional support to manage their HF. (Strength of Evidence = B)

8.3 It is recommended that educational sessions begin with an assessment of current HF knowledge, issues about which the patient wants to learn, and the patient's perceived barriers to change. Education sessions should address specific issues (eg, medication nonadherence) and their causes (eg, lack of knowledge vs cost vs forgetting) and employ strategies that promote behavior change, including motivational approaches. (Strength of Evidence = B)

8.4 It is recommended that the frequency and intensity of patient education and counseling vary according to the stage of illness. Patients in advanced HF or with persistent difficulty adhering to the recommended regimen require the most education and counseling. Patients should be offered a variety of options for learning about HF according to their individual preferences:

- Videotape
- One-on-one or group discussion
- Reading materials, translators, telephone calls, mailed information
- Internet
- Visits

Repeated exposure to material is recommended because a single session is never sufficient. (Strength of Evidence = B)

8.5 It is recommended that during the care process patients be asked to:

- Demonstrate knowledge of the name, dose, and purpose of each medication
- Sort foods into high- and low-sodium categories
- Demonstrate their preferred method for tracking medication dosing
- Show provider daily weight log
- Reiterate symptoms of worsening HF
- Reiterate when to call the provider because of specific symptoms or weight changes. (Strength of Evidence = B)

8.6 During acute care hospitalization, only essential education is recommended, with the goal of assisting patients to understand HF, the goals of its treatment, and the post-hospitalization medication and follow-up regimen. Education begun during hospitalization should be supplemented and reinforced within 1-2 weeks after discharge, continued for 3-6 months, and reassessed periodically. (Strength of Evidence = B)

Recommendations for Disease Management Programs

Practitioners who care for patients with HF are challenged daily with preventing common, recurrent rehospitalizations for exacerbations. Disease management is "a comprehensive, integrated system for managing patients…by using best practices, clinical practice improvement…and other resources and tools to reduce overall cost and improve measurable outcomes in the quality of care."[83] A number of disease management programs have been studied, including HF clinics,[84-100] care delivered in the home or to patients who are at home,[101-117] and telemonitoring.[118-124] These programs focus on multiple aspect of patient care, including optimization of drug

Table 8.1. Essential Elements of Patient Education With Associated Skills and Target Behaviors

Elements of Education	Skill Building and Critical Target Behaviors
Definition of HF (linking disease, symptoms, and treatment) and cause of patient's HF	• Discuss basic HF information, cause of patient's HF, and how symptoms relate to HF status
Recognition of escalating symptoms and concrete plan for response to particular symptoms	• Identify specific signs and symptoms (eg, increasing fatigue or shortness of breath with usual activities, dyspnea at rest, nocturnal dyspnea or orthopnea, edema) • Perform daily weights and know how to respond to evidence of volume overload • Develop action plan for how and when to notify the provider, changes to make in diet, fluid and diuretics
Indications and use of each medication	• Reiterate medication dosing schedule, basic reason for specific medications, and what to do if a dose is missed
Modify risks for HF progression	• Smoking cessation • Maintain blood pressure in target range • Maintain normal HgA1c, if diabetic • Maintain specific body weight
Specific diet recommendations: individualized low-sodium diet; recommendation for alcohol intake	• Understand and comply with sodium restriction • Demonstrate how to read a food label to check sodium amount per serving and sort foods into high- and low-sodium groups • Reiterate limits for alcohol consumption or need for abstinence if history of alcohol abuse
Specific activity/exercise recommendations	• Comply with prescribed exercise
Importance of treatment adherence and behavioral strategies to promote	• Plan and use a medication system that promotes routine adherence • Plan for refills

therapy, patient and family/caregiver education and counseling, emphasis on self-care, vigilant follow-up, early attention to signs and symptoms of fluid overload, coordination of care with other providers, quality assessment, and increased access to the health care provider.

8.7 Patients recently hospitalized for HF and other patients at high risk for HF decompensation should be considered for comprehensive HF disease management. High-risk patients include those with renal insufficiency, low output state, diabetes, chronic obstructive pulmonary disease, persistent NYHA class III or IV symptoms, frequent hospitalization for any cause, multiple active comorbidities, or a history of depression, cognitive impairment, inadequate social support, poor health literacy, or persistent nonadherence to therapeutic regimens. (Strength of Evidence = A)

8.8 It is recommended that HF disease management programs include the components shown in Table 8.3 based on patient characteristics and needs. (Strength of Evidence = B)

Table 8.3. Recommended Components of a HF Disease Management Program

- Comprehensive education and counseling individualized to patient needs
- Promotion of self care, including self-adjustment of diuretic therapy in appropriate patients (or with family member/caregiver assistance)
- Emphasis on behavioral strategies to increase adherence
- Vigilant follow-up after hospital discharge or after periods of instability
- Optimization of medical therapy
- Increased access to providers
- Early attention to signs and symptoms of fluid overload
- Assistance with social and financial concerns

8.9 It is recommended that HF disease management include integration and coordination of care between the primary care physician and HF care specialists and with other agencies, such as home health and cardiac rehabilitation. (Strength of Evidence = C)

8.10 It is recommended that patients in a HF disease management program be followed until they or their family/caregiver demonstrate independence in following the prescribed treatment plan, adequate or improved adherence to treatment guidelines, improved functional capacity, and symptom stability. Higher risk patients with more advanced HF may need to be followed permanently. Patients who experience increasing episodes of exacerbation or who demonstrate instability after discharge from a program should be referred again to the service. (Strength of Evidence = B)

Recommendations for Advance Directives and End-of-Life Care

HF has a worse prognosis than many common cancers,[125] and premature death from progressive acute decompensated heart failure (ADHF) or SCD is frequent. Recent advances in HF treatment have resulted in substantial reductions in annual mortality from these modes of death. Nevertheless, the mortality rate in HF remains high, making advance directives and end-of-life care important issues for patients with this condition. Hospice services or other end-of-life care should only be implemented after full and appropriate application of evidence-based pharmacologic and cardiac device

therapies, unless documentation of intolerance or contraindication to such treatments is present. For critically ill patients, clinicians should acknowledge to the patient and their family the potentially life-threatening nature of their condition, and supportive care for them should be implemented as indicated. In most cases, adequate time (weeks to months) must be given to allow medical therapies to exert a beneficial therapeutic effect. In addition, issues such as access to care, adherence to medications and other self care behaviors, and knowledge about HF must be addressed. End-of-life care most often includes continuing HF therapies, which may effectively ease symptoms and stabilize or improve quality of life. A discussion about HF course and prognosis should be conducted with all patients to the extent that they are willing to participate in such a conversation. Discussion of end-of-life care can occur when the patient has progressed to a state of severe, refractory HF.

8.11 It is recommended that patient and family or caregiver discussions about quality of life and prognosis be included in the disease management of HF. (Strength of Evidence = C)

8.12 It is recommended that:

a. Seriously ill patients with HF and their families be educated to understand that patients with HF are at high risk of death, even while aggressive efforts are made to prolong life.

b. Patients with HF be made aware that HF is potentially life-limiting, but that pharmacologic and device therapies and self-management can prolong life. In most cases, chronic HF pharmacologic and device therapies should be optimized as indicated before identifying that patients are near end-of-life.

c. Identification of end-of-life in a patient should be made in collaboration with clinicians experienced in the care of patients with HF when possible.

d. End-of-life management should be coordinated with the patient's primary care physician.

e. As often as possible, discussions regarding end-of-life care should be initiated while the patient is still capable of participating in decision-making. (Strength of Evidence = C)

8.13 End-of-life care should be considered in patients who have advanced, persistent HF with symptoms at rest despite repeated attempts to optimize pharmacologic, cardiac device, and other therapies, as evidenced by 1 or more of the following:

- HF hospitalization [126,127] (Strength of Evidence = B)
- Chronic poor quality of life with minimal or no ability to accomplish activities of daily living (Strength of Evidence = C)
- Need for continuous intravenous inotropic therapy support [128,129] (Strength of Evidence = B)

8.14 It is recommended that end-of-life care strategies be individualized and include core HF pharmacologic therapies, effective symptom management and comfort measures, while avoiding unnecessary testing. New life-prolonging interventions should be discussed with patients and care-givers with careful discussion of whether they are likely to improve symptoms. (Strength of Evidence = C)

8.15 It is recommended that a specific discussion about resuscitation be held in the context of planning for overall care and for emergencies with all patients with HF. The possibility of SCD for patients with HF should be acknowledged. Specific plans to reduce SCD (for example with an ICD) or to allow natural death should be based on the individual patient's risks and preferences for an attempt at resuscitation with specific discussion of risks and benefits of inactivation the ICD. Preferences for attempts at resuscitation and plans for approach to care should be readdressed at turning points in the patient's course or if potentially life-prolonging interventions are considered. (Strength of Evidence = C)

8.16 It is recommended that, as part of end-of-life care, patients and their families/caregivers have a plan to manage a sudden decompensation, death, or progressive decline. Inactivation of an implantable defibrillation device should be discussed in the context of allowing natural death at end of life. A process for deactivating defibrillators should be clarified in all settings in which patients with HF receive care. (Strength of Evidence = C)

8.17 Patients with HF receiving end-of-life care should be considered for enrollment in hospice that can be delivered in the home, a nursing home, or a special hospice unit. (Strength of Evidence = C)

Section 9: Electrophysiology Testing and the Use of Devices in Heart Failure

Device therapy has become an integral part of the treatment for HF. Appropriate patient selection in terms of HF characteristics, severity, and other comorbidities is a key consideration to ensure the optimal application of this therapy.

Recommendations for General Electrophysiology Testing

9.1 It is recommended that the decision to undertake electrophysiologic intervention, including implantable cardioverter defibrillator (ICD) implantation, be made in light of functional status and prognosis based on severity of underlying HF and comorbid conditions. If an ICD is considered due to left ventricular (LV) dysfunction which is of recent onset, LV

function should be reassessed, ideally after 3-6 months of optimal medical therapy. (Strength of Evidence = C)

Recommendations for Electrophysiology Testing and Evaluation of Syncope

9.2 Immediate evaluation is recommended in patients with HF who present with syncope. In the absence of a clear identifiable noncardiac cause, consultation with an EP specialist should be obtained. (Strength of Evidence = C)

9.3 Routine EP testing is not recommended in patients with LV systolic dysfunction who have asymptomatic nonsustained ventricular tachycardia (VT) in the absence of prior infarction. (Strength of Evidence = B)

Recommendations for Prophylactic ICD Placement

More than 80 percent of patients who experience a life-threatening ventricular tachyarrhythmia do not survive to benefit from an ICD. Thus, the concept of the ICD for primary prevention of SCD has received considerable attention. Several large trials have demonstrated efficacy of prophylactic ICDs in certain patient groups.[130-135]

9.4a Prophylactic ICD placement should be considered in patients with an LVEF ≤35% and mild to moderate HF symptoms:
- Ischemic etiology (Strength of Evidence = A)
- Non-ischemic etiology (Strength of Evidence = B)

See Recommendation 9.1 for additional criteria.

9.4b In patients who are undergoing implantation of a biventricular pacing device according to the criteria in recommendations 9.7-9.8, use of a device that provides defibrillation should be considered. (Strength of Evidence = B)

See Recommendation 9.1 for additional criteria.

9.5 ICD placement is not recommended in chronic, severe refractory HF when there is no reasonable expectation for improvement or in patients with a life expectancy of less than 1 year. (Strength of Evidence = C)

9.6 ICD implantation is recommended for survivors of cardiac arrest from ventricular fibrillation or hemodynamically unstable sustained VT that is not due to a transient, potentially reversible cause, such as acute MI. (Strength of Evidence = A)

Recommendations for Biventricular Resynchronization Pacing

The majority of patients with HF have interventricular conduction delay, and up to 30% to 50% have manifest bundle branch block caused by direct pathologic involvement of specialized conduction or by scarring of the myocardium.[136] CRT seeks to normalize depolarization to improve the efficiency of ventricular contraction and ventricular septal motion, decrease atrioventricular valve regurgitation, and increase diastolic filling time.[137]

9.7 Biventricular pacing therapy is recommended for patients in sinus rhythm with a widened QRS interval (≥120 ms) and severe LV systolic dysfunction (LVEF ≤ 35%) who have persistent, moderate to severe HF (NYHA III) despite optimal medical therapy. (Strength of Evidence = A)

9.8 Biventricular pacing therapy may be considered for patients with atrial fibrillation with a widened QRS interval (≥120 ms) and severe LV systolic dysfunction LVEF ≤35% who have persistent, moderate to severe HF (NYHA III) despite optimal medical therapy. (Strength of Evidence = B)

9.9 Selected ambulatory NYHA IV patients in sinus rhythm with QRS ≥120 ms and LV systolic dysfunction may be considered for biventricular pacing therapy. (Strength of Evidence = B)

9.10 Biventricular pacing therapy may be considered in patients with reduced LVEF and QRS ≥ 150 ms who have NYHA I or II HF symptoms. (Strength of Evidence = B)

9.11 In patients with reduced LVEF who require chronic pacing and in whom frequent ventricular pacing is expected, biventricular pacing may be considered. (Strength of Evidence = C)

Recommendations for Dual Chamber Pacemakers

9.12 The routine use of dual (atrioventricular [AV]) chamber pacemakers for HF in the absence of symptomatic bradycardia or high-grade AV block is not recommended. (Strength of Evidence = A)

Section 10: Surgical Approaches to the Treatment of Heart Failure

Despite advances in medical management of HF, there remain circumstances in which surgical procedures are the only or the best treatment option. These include heart transplantation and procedures that (1) repair the heart, (2) reshape it, or (3) replace all or part of heart function.

Recommendations for Surgical Approaches

10.1 It is recommended that the decision to undertake surgical intervention for severe HF be made in light of functional status and prognosis based on severity of underlying HF and comorbid conditions. Procedures

should be done at centers with demonstrable expertise and multidisciplinary medical and surgical teams experienced in the selection, care, and perioperative and long-term management of high risk patients with severe HF. (Strength of Evidence = C)

10.2 Evaluation for heart transplantation is recommended in selected patients with severe HF, debilitating refractory angina, or ventricular arrhythmia that cannot be controlled despite drug, device, or alternative surgical therapy. (Strength of Evidence = B)

10.3 Isolated mitral valve repair or replacement for severe mitral regurgitation secondary to ventricular dilatation in the presence of severe left ventricular (LV) systolic dysfunction is not generally recommended. (Strength of Evidence = C)

10.4 Partial LV resection ("Batista procedure") is not recommended in nonischemic cardiomyopathy. (Strength of Evidence = B)

10.5 Patients awaiting heart transplantation who have become refractory to all means of medical circulatory support should be considered for a mechanical support device as a bridge to transplant. (Strength of Evidence = B)

10.6 Permanent mechanical assistance using an implantable assist device may be considered in highly selected patients with severe HF refractory to conventional therapy who are not candidates for heart transplantation, particularly those who cannot be weaned from intravenous inotropic support at an experienced HF center. (Strength of Evidence = B)

10.7 Patients with refractory HF and hemodynamic instability, and/or compromised end-organ function, with relative contraindications to cardiac transplantation or permanent mechanical circulatory assistance expected to improve with time or restoration of an improved hemodynamic profile should be considered for urgent mechanical circulatory support as a ''bridge to decision.'' These patients should be referred to a center with expertise in the management of patients with advanced HF. (Strength of Evidence = C)

Section 11: Evaluation and Management of Patients With Heart Failure and Preserved Left Ventricular Ejection Fraction

A substantial number of patients with HF have preserved LVEF, variably defined as an LVEF >40%, >45%, or >50%.[138,139] When these patients have invasive or non-invasive evidence of abnormal diastolic function (either abnormal relaxation, filling or stiffness) they are said to have ''diastolic HF''.[140] Although the term ''HF with normal LVEF'' is often used to denote this group, because ''normal'' is variously defined, ''HF with preserved LVEF'' will be the active definition in this document. The left ventricle in HF with preserved LVEF may be characterized by LV hypertrophy,[141] concentric remodeling, increased extracellular matrix,[142] abnormal calcium handling, abnormal relaxation and filling and decreased diastolic distensibility.[143,144] Activation of the neurohormonal milieu, including the RAAS and the sympathetic nervous system, is common in HF with and without preserved LVEF.[144]

Recommendations for Patients With Heart Failure and Preserved LVEF

11.1 Careful attention to differential diagnosis is recommended in patients with HF and preserved LVEF to distinguish among a variety of cardiac disorders, because treatments may differ. These various entities may be distinguished based on echocardiography, electrocardiography, and stress imaging (via exercise or pharmacologic means, using myocardial perfusion or echocardiographic imaging) and cardiac catheterization. See complete guideline Section 11 for Figures 11.1, 11.2, and 11.3 for guidance to a differential diagnosis. (Strength of Evidence = C)

11.2 Evaluation for ischemic heart disease and inducible myocardial ischemia is recommended in patients with HF and preserved LVEF (see Section 13). (Strength of Evidence = C)

11.3 Blood pressure monitoring is recommended in patients with HF and preserved LVEF (Section 14, Recommendation 14.1). (Strength of Evidence = C)

11.4 Counseling on the use of a low-sodium diet (Section 6) is recommended for all patients with HF, including those with preserved LVEF. (Strength of Evidence = C)

11.5 Diuretic treatment is recommended in all patients with HF and clinical evidence of volume overload, including those with preserved LVEF. Treatment may begin with either a thiazide or loop diuretic. In more severe volume overload or if response to a thiazide is inadequate, treatment with a loop diuretic should be implemented. Excessive diuresis, which may lead to orthostatic changes in blood pressure and worsening renal function, should be avoided. (Strength of Evidence = C)

11.6 In the absence of other specific indications for these drugs, angiotensin receptor blockers (ARBs) or angiotensin converting enzyme (ACE) inhibitors may be considered in patients with HF and preserved LVEF.

- ARBs (Strength of Evidence = C)
- ACE inhibitors (Strength of Evidence = C)

11.7 ACE inhibitors should be considered in all patients with HF and preserved LVEF who have symptomatic atherosclerotic cardiovascular disease or diabetes

and one additional risk factor. (Strength of Evidence = C)

In patients who meet these criteria but are intolerant to ACE inhibitors, ARBs should be considered. (Strength of Evidence = C)

11.8 Beta blocker treatment is recommended in patients with HF and preserved LVEF who have:

- Prior myocardial infarction (Strength of Evidence = A)
- Hypertension (see Section 14) (Strength of Evidence = B)
- Atrial fibrillation requiring control of ventricular rate (Strength of Evidence = B)

11.9 Calcium channel blockers should be considered in patients with HF and preserved LVEF and:

- Atrial fibrillation requiring control of ventricular rate and intolerance to beta blockers. In these patients, diltiazem or verapamil should be considered. (Strength of Evidence = C)
- Symptom-limiting angina. (Strength of Evidence = A)
- Hypertension. (Strength of Evidence = C)

11.10 Measures to restore and maintain sinus rhythm may be considered in patients who have symptomatic atrial flutter-fibrillation and preserved LVEF, but this decision should be individualized. (Strength of Evidence = C)

Section 12: Evaluation and Management of Patients With Acute Decompensated Heart Failure

Data from several studies have refined our understanding of the clinical characteristics of patients hospitalized with worsening HF.[145-148] These studies demonstrate that the majority of patients hospitalized with HF have evidence of systemic hypertension on admission and commonly have preserved LVEF. Most hospitalized patients have significant volume overload, and congestive symptoms predominate. Patients with severely impaired systolic function, reduced blood pressure, and symptoms from poor end-organ perfusion are in the distinct minority. Natural history studies have shown that ADHF represents a period of high risk for patients, during which their likelihood of death and rehospitalization is significantly greater than for a comparable period of chronic, but stable HF.[146]

The clinical classification of patients with ADHF continues to evolve and reflects ongoing changes in our understanding of the pathophysiology of this syndrome.[149] Worsening renal function, persistent neurohormonal activation, and progressive deterioration in myocardial function all seem to play a role. Decompensation also commonly occurs without a fundamental worsening of underlying cardiac structure or function. Failure to adhere to prescribed medications related to inadequate financial resources, poor compliance, and lack of education or an inadequate medical regimen may lead to hospitalization without a worsening of underlying circulatory function.

There is a paucity of controlled clinical trial data to define optimal treatment for patients with ADHF. The few trials have focused primarily on symptom relief, not outcomes, and have mainly enrolled patients with reduced LVEF who were not hypertensive. Clinical studies to determine the best care processes to achieve the multiple goals for patients admitted with ADHF are lacking. The recommendations in this section address the common therapeutic dilemmas associated with the broad group of patients with ADHF using the best available evidence from clinical research and consensus expert opinion.

Recommendations for Acute Decompensated Heart Failure

12.1 The diagnosis of Acute Decompensated HF should be based primarily on signs and symptoms. (Strength of Evidence = C)

When the diagnosis is uncertain, determination of B-type natriuretic peptide (BNP) or N-terminal pro-B-type natriuretic peptide (NT-proBNP) concentration is recommended in patients being evaluated for dyspnea who have signs and symptoms compatible with HF. (Strength of Evidence = A)

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, and with the knowledge of cardiac and non-cardiac factors that can raise or lower natriuretic peptide levels.

12.2 Hospital admission is recommended for patients presenting with ADHF when the clinical circumstances listed in Table 12.1(a) are present. Patients presenting with ADHF should be considered for hospital admission when the clinical circumstances listed in Table 12.1(b) are present. (Strength of Evidence = C)

12.3 It is recommended that patients admitted with ADHF be treated to achieve the goals listed in Table 12.3. (Strength of Evidence = C)

12.4 Patients admitted with ADHF should be carefully monitored. It is recommended that the items listed in Table 12.4 be assessed at the stated frequencies. (Strength of Evidence = C)

12.5 It is recommended that patients admitted with ADHF and evidence of fluid overload be treated initially with loop diuretics - usually given intravenously rather than orally. (Strength of Evidence = B)

Ultrafiltration may be considered in lieu of diuretics. (Strength of Evidence = B)

12.6 It is recommended that diuretics be administered at doses needed to produce a rate of diuresis sufficient

Table 12.1. Recommendations for Hospitalizing Patients Presenting With ADHF

Recommendation	Clinical Circumstances
(a) Hospitalization Recommended	Evidence of severe ADHF, including:
	Hypotension
	Worsening renal function
	Altered mentation
	Dyspnea at rest
	Typically reflected by resting tachypnea
	Less commonly reflected by oxygen saturation <90%
	Hemodynamically significant arrhythmia
	Including new onset of rapid atrial fibrillation
	Acute coronary syndromes
(b) Hospitalization Should Be Considered	Worsened congestion
	Even without dyspnea
	Signs and symptoms of pulmonary or systemic congestion
	Even in the absence of weight gain
	Major electrolyte disturbance
	Associated comorbid conditions
	Pneumonia
	Pulmonary embolus
	Diabetic ketoacidosis
	Symptoms suggestive of transient ischemic accident or stroke
	Repeated ICD firings
	Previously undiagnosed HF with signs and symptoms of systemic or pulmonary congestion

Table 12.4. Monitoring Recommendations for Patients Hospitalized With ADHF

Frequency	Value	Specifics
At least daily	Weight	Determine after voiding in the morning
		Account for possible increased food intake due to improved appetite
At least daily	Fluid intake and output	
More than daily	Vital signs	Orthostatic blood pressure if indicated
		Oxygen saturation daily until stable
At least daily	Signs	Edema
		Ascites
		Pulmonary rales
		Hepatomegaly
		Increased JVP
		Hepatojugular reflux
		Liver tenderness
At least daily	Symptoms	Orthopnea
		Paroxysmal nocturnal dyspnea (PND) or cough
		Nocturnal cough
		Dyspnea
		Fatigue, lightheadedness
At least daily	Electrolytes	Potassium
		Sodium
At least daily	Renal function	BUN
		Serum creatinine*

*See background section for additional recommendations on laboratory evaluations.

to achieve optimal volume status with relief of signs and symptoms of congestion (edema, elevated JVP, dyspnea), without inducing an excessively rapid reduction in 1) intravascular volume, which may result in symptomatic hypotension and/or worsening renal function, or 2) serum electrolytes, which may precipitate arrhythmias or muscle cramps. (Strength of Evidence = C)

12.7 Careful repeated assessment of signs and symptoms of congestion and changes in body weight is recommended, because clinical experience suggests it is difficult to determine that congestion has been adequately treated in many patients. (Strength of Evidence = C)

Table 12.3. Treatment Goals for Patients Admitted for ADHF

Improve symptoms, especially congestion and low-output symptoms
Restore normal oxygenation
Optimize volume status
Identify etiology (see Table 4.6)
Identify and address precipitating factors
Optimize chronic oral therapy
Minimize side effects
Identify patients who might benefit from revascularization
Identify patients who might benefit from device therapy
Identify risk of thromboembolism and need for anticoagulant therapy
Educate patients concerning medications and self management of HF
Consider and, where possible, initiate a disease management program

12.8 Monitoring of daily weights, intake, and output is recommended to assess clinical efficacy of diuretic therapy. Routine use of a Foley catheter is not recommended for monitoring volume status. However, placement of a catheter is recommended when close monitoring of urine output is needed or if a bladder outlet obstruction is suspected of contributing to worsening renal function. (Strength of Evidence = C)

12.9 Careful observation for development of a variety of side effects, including renal dysfunction, electrolyte abnormalities, symptomatic hypotension, and gout is recommended in patients treated with diuretics, especially when used at high doses and in combination. Patients should undergo routine laboratory studies and clinical examination as dictated by their clinical response. (Strength of Evidence = C)

It is recommended that serum potassium and magnesium levels be monitored at least daily and maintained in the normal range. More frequent monitoring may be necessary when diuresis is rapid. (Strength of Evidence = C)

Overly rapid diuresis may be associated with severe muscle cramps. If indicated, treatment with potassium replacement is recommended. (Strength of Evidence = C)

12.10 Careful observation for the development of renal dysfunction is recommended in patients treated with diuretics. Patients with moderate to severe renal dysfunction and evidence of fluid retention should continue to be treated with diuretics. In the presence of severe fluid overload, renal dysfunction may improve with diuresis. (Strength of Evidence = C)

12.11 When congestion fails to improve in response to diuretic therapy, the following options should be considered:

- Re-evaluating presence/absence of congestion
- Sodium and fluid restriction,
- Increasing doses of loop diuretic,
- Continuous infusion of a loop diuretic, or
- Addition of a second type of diuretic orally (metolazone or spironolactone) or intravenously (chlorothiazide).

Another option, ultrafiltration, may be considered. (Strength of Evidence = C)

12.12 A low sodium diet (2 g daily) is recommended for most hospitalized patients. (Strength of Evidence = C)

In patients with recurrent or refractory volume overload, stricter sodium restriction may be considered. (Strength of Evidence = C)

12.13 Fluid restriction (<2 L/day) is recommended in patients with moderate hyponatremia (serum sodium <130 mEq/L) and should be considered to assist in treatment of fluid overload in other patients. (Strength of Evidence = C)

In patients with severe (serum sodium <125 mEq/L) or worsening hyponatremia, stricter fluid restriction may be considered. (Strength of Evidence = C)

12.14 Routine administration of supplemental oxygen in the presence of hypoxia is recommended. (Strength of Evidence = C)

Routine administration of supplemental oxygen in the absence of hypoxia is not recommended. (Strength of Evidence = C)

12.15 Use of non-invasive positive pressure ventilation may be considered for severely dyspneic patients with clinical evidence of pulmonary edema. (Strength of Evidence = A)

12.16 Venous thromboembolism prophylaxis with low dose unfractionated heparin (UFH), low molecular weight heparin (LMWH), or fondaparinux to prevent proximal deep venous thrombosis (DVT) and pulmonary embolism (PE) is recommended for patients who are admitted to the hospital with ADHF and who are not already anticoagulated and have no contraindication to anticoagulation. (Strength of Evidence = B)

Venous thromboembolism prophylaxis with a mechanical device (intermittent pneumatic compression devices or graded compression stockings) to prevent proximal DVT and PE should be considered for patients who are admitted to the hospital with ADHF and who are not already anticoagulated and who have a contraindication to anticoagulation. (Strength of Evidence = C)

12.17 In the absence of symptomatic hypotension, intravenous nitroglycerin, nitroprusside or nesiritide may be considered as an addition to diuretic therapy for rapid improvement of congestive symptoms in patients admitted with ADHF. (Strength of Evidence = B)

Frequent blood pressure monitoring is recommended with these agents. (Strength of Evidence = B)

These agents should be decreased in dosage or discontinued if symptomatic hypotension or worsening renal function develops. (Strength of Evidence = B)

Reintroduction in increasing doses may be considered once symptomatic hypotension is resolved. (Strength of Evidence = C)

12.18 Intravenous vasodilators (nitroglycerin or nitroprusside) and diuretics are recommended for rapid symptom relief in patients with acute pulmonary edema or severe hypertension. (Strength of Evidence = C)

12.19 Intravenous vasodilators (nitroprusside, nitroglycerin, or nesiritide) may be considered in patients with ADHF who have persistent severe HF despite aggressive treatment with diuretics and standard oral therapies.

- Nitroprusside (Strength of Evidence = B)
- Nitroglycerine, Nesiritide (Strength of Evidence = C)

12.20 Intravenous inotropes (milrinone or dobutamine) may be considered to relieve symptoms and improve end-organ function in patients with advanced HF characterized by LV dilation, reduced LVEF, and diminished peripheral perfusion or end-organ dysfunction (low output syndrome), particularly if these patients have marginal systolic blood pressure (<90 mm Hg), have symptomatic hypotension despite adequate filling pressure, or are unresponsive to, or intolerant of, intravenous vasodilators. (Strength of Evidence = C)

These agents may be considered in similar patients with evidence of fluid overload if they respond poorly to intravenous diuretics or manifest diminished or worsening renal function. (Strength of Evidence = C)

When adjunctive therapy is needed in other patients with ADHF, administration of vasodilators

should be considered instead of intravenous inotropes (milrinone or dobutamine). (Strength of Evidence = C)

Intravenous inotropes (milrinone or dobutamine) are not recommended unless left heart filling pressures are known to be elevated or cardiac index is severely impaired based on direct measurement or clear clinical signs. (Strength of Evidence = C)

It is recommended that administration of intravenous inotropes (milrinone or dobutamine) in the setting of ADHF be accompanied by continuous or frequent blood pressure monitoring and continuous monitoring of cardiac rhythm. (Strength of Evidence = C)

If symptomatic hypotension or worsening tachyarrhythmias develop during administration of these agents, discontinuation or dose reduction should be considered. (Strength of Evidence = C)

12.21 The routine use of invasive hemodynamic monitoring in patients with ADHF is not recommended. (Strength of Evidence = A)

12.22 Invasive hemodynamic monitoring should be considered in a patient:

- who is refractory to initial therapy,
- whose volume status and cardiac filling pressures are unclear,
- who has clinically significant hypotension (typically SBP <80 mm Hg) or worsening renal function during therapy, or
- who is being considered for cardiac transplant and needs assessment of degree and reversibility of pulmonary hypertension, or
- in whom documentation of an adequate hemodynamic response to the inotropic agent is necessary when chronic outpatient infusion is being considered. (Strength of Evidence = C)

12.23 It is recommended that patients admitted with ADHF undergo evaluation for the following precipitating factors: atrial fibrillation or other arrhythmias (eg, atrial flutter, other supraventricular VT or VT), exacerbation of hypertension, myocardial ischemia/infarction, exacerbation of pulmonary congestion, anemia, thyroid disease, significant drug interactions, and other less common factors. (Strength of Evidence = C)

12.24 It is recommended that every effort be made to use the hospital stay for assessment and improvement of patient adherence via patient and family education and social support services (see Section 8). (Strength of Evidence = B)

Table 12.7. Discharge Criteria for Patients With HF

Recommended for all HF patients	• Exacerbating factors addressed. • Near optimal volume status observed. • Transition from intravenous to oral diuretic successfully completed. • Patient and family education completed, including clear discharge instructions • LVEF documented • Smoking cessation counseling initiated • Near optimal pharmacologic therapy achieved, including ACE inhibitor and beta blocker (for patients with reduced LVEF), or intolerance documented (Sections 7 and 11) • Follow-up clinic visit scheduled, usually for 7-10 days
Should be considered for patients with advanced HF or recurrent admissions for HF	• Oral medication regimen stable for 24 hours • No intravenous vasodilator or inotropic agent for 24 hours • Ambulation before discharge to assess functional capacity after therapy • Plans for postdischarge management (scale present in home, visiting nurse or telephone follow up generally no longer than 3 days after discharge) • Referral for disease management, if available

12.25 It is recommended that criteria in Table 12.7 be met before a patient with HF is discharged from the hospital. (Strength of Evidence = C)

In patients with advanced HF or recurrent admissions for HF, additional criteria listed in Table 12.7 should be considered. (Strength of Evidence = C)

12.26 Discharge planning is recommended as part of the management of patients with ADHF. Discharge planning should address the following issues:

- Details regarding medication, dietary sodium restriction, and recommended activity level
- Follow-up by phone or clinic visit early after discharge to reassess volume status
- Medication and dietary compliance
- Alcohol moderation and smoking cessation
- Monitoring of body weight, electrolytes and renal function
- Consideration of referral for formal disease management. (Strength of Evidence = C)

Section 13: Evaluation and Therapy for Heart Failure in the Setting of Ischemic Heart Disease

The most common cause of chronic HF is no longer hypertension or valvular heart disease; it is CAD.[2] The changing pattern in the risk factors for HF is evidenced in the

Framingham Heart Study, which documents a decrease in valvular disease and LV hypertrophy and an increase in MI from 1950 to 1998.[3] As survival from MI continues to improve, it is expected that the number of patients with CAD and HF will also increase.

HF in the setting of CAD is a heterogeneous condition with several factors contributing to LV systolic dysfunction and HF symptoms. After an MI, there is loss of functioning myocytes, development of myocardial fibrosis, and subsequent LV remodeling, resulting in chamber dilatation and neurohormonal activation - all leading to progressive dysfunction of the remaining viable myocardium.[49]

Several studies have shown that CAD is associated with an increase in mortality rates in patients with HF.[30-36] Data also suggest that the mechanism of sudden death may differ between ischemic and nonischemic HF patients, with acute coronary events representing the major cause of sudden death in HF patients with CAD.[38] These findings further emphasize the importance of accurate differentiation between ischemic and nonischemic causes of HF.

Managing HF in patients with CAD or a history of CAD may be significantly different than managing HF due to primary cardiomyopathy. Antiplatelet agents, smoking cessation, and lipid-lowering therapy are particularly important interventions in patients with HF due to CAD.[40] Trials of milrinone,[41] amiodarone,[18] amlodipine,[15] and digoxin suggest that patients with HF in the setting of CAD may have a less favorable outcome than patients with HF from primary cardiomyopathy. Revascularization in highly selected patients with reduced LVEF and significant CAD, particularly those with anginal symptoms, may be associated with improved survival and may be considered in addition to risk modification.[33,42-49]

Recommendations for Heart Failure in the Setting of Ischemic Heart Disease

13.1 Ongoing assessment for risk factors for CAD is recommended in all patients with chronic HF regardless of LVEF. (Strength of Evidence = A)

13.2 It is recommended that the diagnostic approach for CAD be individualized based on patient preference and comorbidities, eligibility, symptoms suggestive of angina and willingness to undergo revascularization. (Strength of Evidence = C)

13.3 It is recommended that patients with HF and symptoms suggestive of angina undergo cardiac catheterization with coronary angiography to assess for potential revascularization. (Strength of Evidence = B)

13.4 It is recommended that, at the initial diagnosis of HF and any time symptoms worsen without obvious cause, patients with HF, no angina, and known CAD should undergo risk assessment that may include noninvasive stress imaging and/or coronary angiography to assess severity of coronary disease and the presence of ischemia. (Strength of Evidence = C)

13.5 It is recommended that patients with HF, no angina, and unknown CAD status who are at high risk for CAD should undergo noninvasive stress imaging and/or coronary angiography to assess severity of coronary disease and the presence of ischemia. (Strength of Evidence = C)

13.6 In patients with HF, no angina, and unknown CAD status who are at low risk for CAD noninvasive evaluation should be considered and coronary angiography may be considered. (Strength of Evidence = C)

13.7 Any of the following imaging tests should be considered to identify inducible ischemia or viable myocardium:

- Exercise or pharmacologic stress myocardial perfusion imaging
- Exercise or pharmacologic stress echocardiography
- Cardiac magnetic resonance imaging (MRI)
- Positron emission tomography scanning (PET).

(Strength of Evidence = B)

13.8 It is recommended that the following risk factors be managed according to the indicated guidelines:

- Lipids (see National Cholesterol Education Program Adult Treatment Panel III) (http://www.nhlbi.nih.gov/guidelines/cholesterol) [92,93]
- Smoking (see Section 3)
- Physical activity (see Section 6)
- Weight (see Section 3)
- Blood pressure (see Section 14 and JNC VII Guidelines) (http://www.nhlbi.nih.gov/guidelines/hypertension) [94]

(See individual guidelines for Strength of Evidence).

13.9 Antiplatelet therapy is recommended to reduce vascular events in patients with HF and CAD unless contraindicated. (aspirin, Strength of Evidence = A; clopidogrel, Strength of Evidence = B)

13.10 ACE inhibitors are recommended in all patients with either reduced or preserved LVEF after an MI. (Strength of Evidence = A)

13.11 Beta blockers are recommended for the management of all patients with reduced LVEF or post-MI. (Strength of Evidence = B)

13.12 It is recommended that ACE-inhibitor and beta blocker therapy be initiated early (<48 hours) during hospitalization in hemodynamically stable post-MI patients with reduced LVEF or HF. (Strength of Evidence = A)

13.13 Nitrate preparations should be considered in patients with HF when additional medication is needed for relief of anginal symptoms. (Strength of Evidence = B)

13.14 Calcium channel blockers may be considered in patients with HF who have angina despite the optimal use of beta blockers and nitrates. Amlodipine and felodipine are the preferred calcium channel blockers in patients with angina and decreased systolic function. Based on available data, first generation calcium channel blockers (i.e. diltiazem, verapamil) should be avoided in patients with CAD, HF, and LVEF <40, unless necessary for heart rate control or other indications. (Strength of Evidence = C)

13.15 It is recommended that coronary revascularization be performed in patients with HF and suitable coronary anatomy for relief of refractory angina or acute coronary syndrome. (Strength of Evidence = B)

13.16 Coronary revascularization with coronary artery bypass surgery or percutaneous coronary intervention (PCI) as appropriate should be considered in patients with HF and suitable coronary anatomy who have demonstrable evidence of myocardial viability in areas of significant obstructive coronary disease or the presence of inducible ischemia. (Strength of Evidence = C)

Section 14: Managing Patients With Hypertension and Heart Failure

Blood pressure is a simple measurement that assesses the interaction of heart function with vascular impedance. When heart function is normal, the impedance is the main determinant of blood pressure. Therefore, pressure (systolic and mean) becomes a powerful risk factor for development of LV hypertrophy, increased myocardial oxygen consumption, coronary atherosclerosis, and subsequent HF.[150,151] Control of blood pressure in this setting is critical to prevent the development and progression of LV dysfunction.[152]

When LV function is impaired, however, the relationship between impedance and cardiac function becomes more complex. Increases of impedance may impair LV emptying and thus not be reflected in a higher pressure. Under those circumstances therapy is aimed at the impedance, not at the blood pressure. Indeed, blood pressure may rise in response to effective therapy that improves LV emptying or reverses remodeling even if the impedance is reduced.

Recommendation for Patients With Hypertension and Preserved LVEF and Asymptomatic LVH, or for Patients With Hypertension and HF With Preserved LVEF (Stage B)

14.1 It is recommended that blood pressure be optimally treated to lower systolic and usually diastolic levels. More than 1 drug may be required. Target resting levels should be $<130/<80$ mm Hg, if tolerated. (Strength of Evidence = A)

Recommendations for Patients With Hypertension and Asymptomatic LV Dysfunction With LV Dilation and a Low LVEF

14.2 Prescription of an angiotensin converting enzyme (ACE) inhibitor (dose equivalent to 20 mg daily enalapril) is recommended (Strength of Evidence = A)

14.3 Addition of a beta blocker (dose equivalent to HF trials) is recommended even if blood pressure is controlled. (Strength of Evidence = C)

14.4 If blood pressure remains $>130/80$ mm Hg then the addition of a thiazide diuretic is recommended, followed by a dihydropyridine calcium antagonist (eg, amlodipine or felodipine) or other antihypertensive drugs. (Strength of Evidence = C)

Recommendations for Patients With Hypertension and Symptomatic LV Dysfunction With LV Dilation and Low LVEF

14.5 Prescription of target doses of ACE inhibitors, angiotensin receptor blockers (ARBs), beta blockers, aldosterone inhibitors, and isosorbide dinitrate/hydralazine in various combinations (with a loop diuretic if needed) is recommended, based on doses used in large-scale outcome trials (see Table 7.1). (Strength of Evidence = A)

14.6 If blood pressure remains $>130/80$ mm Hg, a dihydropyridine calcium antagonist (eg, amlodipine or felodipine) may be considered or other antihypertensive medication doses increased. (Strength of Evidence = C)

Section 15: Management of Heart Failure in Special Populations

HF is a prevalent condition in women, African Americans, and the elderly of both sexes and any race. In the absence of contradictory data, the clinical recommendations based on trial data derived from predominately younger white male study populations have generally been applied equally to these groups. However, there are etiologic and pathophysiologic considerations specific to these groups that warrant attention if care and outcomes are to be optimized. Although a significant number of women and elderly patients with HF have preserved LV systolic function there is little evidence-based data to guide therapy in this group. Other special populations - ethnic groups such as Hispanics, Asians, American Indians, or Pacific Islanders - are important special populations but there are

inadequate data currently available about HF management to discuss these groups individually. Discussion in this section is based primarily on available data from subgroup analyses of randomized HF trials and the results of cohort studies. A substantial amount of the data on drug efficacy comes from studies of patients treated after a recent acute MI.

Recommendations

15.1 As with younger patients, it is recommended that elderly patients, particularly those age >80 years, be evaluated for HF when presenting with symptoms of dyspnea and fatigue. (Strength of Evidence = C)

15.2 Beta blocker and ACE inhibitor therapy is recommended as standard therapy in all elderly patients with HF due to LV systolic dysfunction. (Strength of Evidence = B)

In the absence of contraindications, these agents are also recommended in the very elderly (age >80 years). (Strength of Evidence = C)

15.3 As in all patients, but especially in the elderly, careful attention to volume status, the possibility of symptomatic cerebrovascular disease, and the presence of postural hypotension is recommended during therapy with ACE inhibitors, beta blockers and diuretics. (Strength of Evidence = C)

15.4 Beta blocker therapy is recommended for women with HF from:
- symptomatic LV systolic dysfunction (Strength of Evidence = B)
- asymptomatic LV systolic dysfunction (Strength of Evidence = C)

15.5 ACE inhibitor therapy is recommended as standard therapy in all women with symptomatic or asymptomatic LV systolic dysfunction. (Strength of Evidence = B)

15.6 ARBs are recommended for administration to symptomatic and asymptomatic women with an LVEF ≤ 40% who are intolerant to ACE inhibitors for reasons other than hyperkalemia or renal insufficiency. (Strength of Evidence = A)

15.7 The combination of hydralazine/isosorbide dinitrate is recommended as standard therapy for African American women with moderate to severe HF symptoms who are on background neurohormonal inhibition. (Strength of Evidence = B)

15.8 Beta blockers are recommended as part of standard therapy for African Americans with HF due to:
- symptomatic LV systolic dysfunction (Strength of Evidence = B)
- asymptomatic LV systolic dysfunction (Strength of Evidence = C)

15.9 ACE inhibitors are recommended as part of standard therapy for African-American patients with HF from symptomatic or asymptomatic LV systolic dysfunction. (Strength of Evidence = C)

15.10 ARBs are recommended as substitute therapy for HF in African Americans intolerant of ACE inhibitors. (Strength of Evidence = B)

15.11 A combination of hydralazine and isosorbide dinitrate is recommended as part of standard therapy in addition to beta blockers and ACE-inhibitors for African Americans with LV systolic dysfunction and:
- NYHA class III or IV HF (Strength of Evidence = A)
- NYHA class II HF (Strength of Evidence = B)

Section 16: Myocarditis: Current Treatment

Myocarditis is a distinct clinical entity with a wide variety of cardiac manifestations including HF. Potential etiologies may include toxins, medications, physical agents and, most importantly, infections. The most common forms appear to be postviral in origin. The pathophysiology of myocarditis has been well established in animal models with myocardial damage due not only to direct infection, but also consequent to postinfectious, autoimmune-mediated myocardial inflammatory damage. In humans, ongoing myocardial inflammation may result in dilated cardiomyopathy, restrictive cardiomyopathy, or acute LV failure without dilatation (fulminant myocarditis). Controversy continues to surround the best approach to the management of patients considered to have myocarditis. The following recommendation is based on a review of available data from uncontrolled and controlled evaluations of immunomodulatory therapy for the treatment of myocarditis.

Recommendations

16.1 Routine use of immunosuppressive therapies is not recommended for patients with myocarditis. (Strength of Evidence = A)

16.2 Endomyocardial biopsy should be considered in patients with an acute deterioration of cardiac function of unknown etiology who are unresponsive to medical therapy. (Strength of Evidence = B)

Section 17: Genetic Evaluation of Cardiomyopathy*

The evidence indicating that hypertrophic cardiomyopathy (HCM) has a genetic basis is extensive: HCM is now understood largely to be a genetic disease of contractile proteins, although less commonly, infiltrative etiologies

may also be causative. The evidence supporting a genetic basis for dilated cardiomyopathy (DCM), after other more common causes have been excluded (eg, ischemic disease, hypothyroidism, cardiotoxic agents such as Adriamycin), is now substantial for familial dilated cardiomyopathy (FDC), where FDC is defined as DCM of unknown cause in 2 or more closely related family members. However, whether sporadic DCM has a genetic basis remains an open question, especially when detectable familial disease has been clinically excluded by testing closely related family members. Thus, although some recommendations formulated for the genetic evaluation of cardiomyopathy, such as the need for family history, apply to all entities, other recommendations must be tailored to account for these differences. This is particularly relevant as these guidelines use the generic term ''cardiomyopathy'' to imply possible familial or genetic cause, assuming that all other detectable causes of cardiomyopathy have been ruled out. This is particularly relevant for DCM where multiple nongenetic causes are possible as noted previously. Recent discoveries indicate that arrhythmogenic right ventricular dysplasia/cardiomyopathy (ARVD/C) is largely caused by mutations in genes encoding proteins of the desmosome. Although initially recognized predominantly in the right ventricle, LV involvement in 20% to 40% of patients has prompted the change in nomenclature from ARVD to ARVD/C.[153] Discovering the genetic basis of restrictive cardiomyopathy (RCM) has been more challenging, because RCM is much less common than DCM or HCM, and less commonly presents with familial disease. Left ventricular noncompaction (LVNC) is an anatomic abnormality of LV myocardial development: LV compaction is incomplete, leaving deep trabeculations in the LV myocardium. LVNC was categorized as a specific type of cardiomyopathy by an expert panel in 2006,[154] and some genetic association has been observed. Although initially reported to be a rare condition associated with adverse outcome,[155] more recent reports[156-158] have called into question those preliminary conclusions.[159] Three different echocardiographic criteria have been used for diagnosis.[156] These authors suggested that the diagnostic criteria for LVNC might be too sensitive. Because of the uncertainty of diagnostic standards leading to difficulty clarifying its phenotype, we suggest that the LVNC recommendations in this document be limited to those individuals with only the most prominent disease.

Recommendations for the Genetic Evaluation of Cardiomyopathy

17.1 A careful family history for ≥3 generations is recommended for all patients with cardiomyopathy.

- Hypertrophic cardiomyopathy (Strength of Evidence = A)
- Dilated cardiomyopathy (Strength of Evidence = A)
- Arrhythmogenic right ventricular dysplasia (Strength of Evidence = A)
- Left ventricular noncompaction (Strength of Evidence = A)
- Restrictive cardiomyopathy (Strength of Evidence = B)
- Cardiomyopathies associated with extracardiac manifestations (Strength of Evidence = A)

17.2 Clinical screening for cardiomyopathy in asymptomatic first-degree relatives is recommended.

a. Cardiomyopathy Phenotype

- Hypertrophic cardiomyopathy (Strength of Evidence = A)
- Dilated cardiomyopathy (Strength of Evidence = A)
- Arrhythmogenic right ventricular dysplasia (Strength of Evidence = A)
- Left ventricular noncompaction (Strength of Evidence = B)
- Restrictive cardiomyopathy (Strength of Evidence = B)
- Cardiomyopathies associated with extracardiac manifestations (Strength of Evidence = A)

b. Clinical screening for cardiomyopathy is recommended at intervals (see below) in asymptomatic

Cardiomyopathy Phenotype	Interval if genetic testing is negative and/or if clinical family screening is negative	Screening interval if a mutation is present	Strength of Evidence
Hypertrophic	Every 3 years until 30 years of age, except yearly during puberty; after 30 years, if symptoms develop	Every 3 years until 30 years of age, except yearly during puberty; every 5 years thereafter	B
Dilated	Every 3-5 years beginning in childhood	Yearly in childhood; every 1-3 years in adults	B
ARVD/C	Every 3-5 years after age 10	Yearly after age 10 to 50 years of age	C
LVNC	Every 3 years beginning in childhood	Yearly in childhood; every 1-3 years in adults	C
Restrictive	Every 3-5 years beginning in adulthood	Yearly in childhood; every 1-3 years in adults	C

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at-risk relatives who are known to carry the disease-causing mutation(s). (Strength of Evidence = A)

c. Clinical screening for cardiomyopathy is recommended for asymptomatic at-risk first-degree relatives when genetic testing has not been performed or has not identified a disease-causing mutation. (Strength of Evidence = A)

d. It is recommended that clinical screening consist of:
- History (with special attention to HF symptoms, arrhythmias, presyncope, and syncope)
- Physical examination (with special attention to the cardiac and skeletal muscle systems)
- Electrocardiogram
- Echocardiogram
- CK-MM (at initial evaluation only)
- Signal-averaged electrocardiogram (SAECG) in ARVD only
- Holter monitoring in HCM, ARVD
- Exercise treadmill testing in HCM
- Magnetic resonance imaging in ARVD (Strength of Evidence = B)

e. Clinical screening for cardiomyopathy should be considered at the following times and intervals or at any time that signs or symptoms appear.

f. At-risk first-degree relatives with any abnormal clinical screening tests (regardless of genotype) should be considered for repeat clinical screening at 1 year. (Strength of Evidence = C)

17.3 Evaluation, genetic counseling, and genetic testing of cardiomyopathy patients are complex processes. Referral to centers expert in genetic evaluation and family-based management should be considered. (Strength of Evidence = B)

17.4 Genetic testing should be considered for the one most clearly affected person in a family to facilitate family screening and management.

a. Cardiomyopathy Phenotype
- Hypertrophic cardiomyopathy (Strength of Evidence = A)
- Dilated cardiomyopathy (Strength of Evidence = B)
- Arrhythmogenic right ventricular dysplasia (Strength of Evidence = A)
- Left ventricular noncompaction (Strength of Evidence = C)
- Restrictive cardiomyopathy (Strength of Evidence = C)
- Cardiomyopathies associated with extracardiac manifestations (Strength of Evidence = A)

Cardiomyopathy Phenotype	Gene Tests Available*	Yield of Positive Results
HCM	MYH7, MYBPC3, TNNT2 TNNI3, TPMI, ACTC, MYL2, MYL3	MYH7, MYBPC3 each account for 30%-40% of mutations, TNNT2 for 10%-20%. Genetic cause can be identified in 35%-45% overall; up to 60%-65% when the family history is positive.
DCM	LMNA, MYH7, TNNT2, SCN5A, DES, MYBPC3, TNNI3, TPMI, ACTC, PLN, LDB3 and TAZ	5.5%, 4.2%, 2.9%, for LMNA, MYH7, and TNNT2, respectively. All data are from research cohorts
ARVD	DSP, PKP2, DSG2, DSC2	6%-16%, 11%-43%, 12%-40%, for DSP, PKP2, and DSG2, respectively
LVNC	Uncertain – see discussion	Uncertain – see discussion
RCM	Uncertain – see discussion	Uncertain – see discussion

*GeneTests (www.genetests.org) is a National Institutes of Health-funded resource that lists clinical (and research) molecular genetic testing laboratories for the cardiomyopathies.

b. Specific genes available for screening based on cardiac phenotype

c. Screening for Fabry disease is recommended in all men with sporadic or non-autosomal dominant (no male-to-male) transmission of unexplained cardiac hypertrophy. (Strength of Evidence = B)

17.5 Genetic and family counseling is recommended for all patients and families with cardiomyopathy. (Strength of Evidence = A)

17.6 Medical therapy based on cardiac phenotype is recommended (see section 7). (Strength of Evidence = A)

17.7 Device therapies for arrhythmia and conduction system disease based on cardiac phenotype are recommended (see section 9). (Strength of Evidence = B)

17.8 In patients with cardiomyopathy and significant arrhythmia or known risk of arrhythmia an ICD may be considered before the LVEF falls below 35%. (Strength of Evidence = C)

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Disclosures

See Appendix C.

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Appendix A. Comparison of the 2006 and 2010 HFSA Guideline

	2006 Guideline Recommendation	2010 Guideline Recommendation	Comments
	Section 3: Prevention of Ventricular Remodeling, Cardiac Dysfunction, and Heart Failure		
3.1	A careful and thorough clinical assessment, with appropriate investigation for known or potential risk factors, is recommended in an effort to prevent development of LV remodeling, cardiac dysfunction, and HF. These risk factors include, but are not limited to, hypertension, hyperlipidemia, atherosclerosis, diabetes mellitus, valvular disease, obesity, physical inactivity, excessive alcohol intake, and smoking. (Strength of Evidence = A)	A careful and thorough clinical assessment, with appropriate investigation for known or potential risk factors, is recommended in an effort to prevent development of LV remodeling, cardiac dysfunction, and HF. These risk factors include, but are not limited to, hypertension, hyperlipidemia, atherosclerosis, diabetes mellitus, valvular disease, obesity, physical inactivity, excessive alcohol intake, dietary choices, and smoking. (Strength of Evidence = A)	Addition of dietary choices to list of risk factors
3.2	No changes		
3.3	No changes		
3.4	No changes		
	Section 4: Evaluation of Patients for Ventricular Dysfunction and Heart Failure		
4.1	Evaluation with a routine history, physical examination, chest x-ray, and electrocardiogram (ECG) is recommended in patients with the medical conditions or test findings listed in Table 4.1. (Strength of Evidence = B)	Evaluation for clinical manifestations of HF with a routine history and physical examination is recommended in patients with the medical conditions or test findings listed in Table 4.1. (Strength of Evidence = B)	Modification of wording and deletion of chest x-ray and ECG (retained in Table 4.1)
4.2	Assessment of Cardiac Structure and Function. Echocardiography with Doppler is recommended to determine LV size and function in patients without signs or symptoms suggestive of HF who have the risk factors listed in Table 4.2. (Strength of Evidence = B)	Assessment of Cardiac Structure and Function. Echocardiography with Doppler is recommended to determine cardiac structure and function in asymptomatic patients with the disorders or findings listed in Table 4.2. (Strength of Evidence = B)	Modification of wording and terminology
4.3	Determination of plasma B-type natriuretic peptide (BNP) or N-terminal pro-BNP concentration is not recommended as a routine part of the evaluation for structural heart disease in patients at risk but without signs or symptoms of HF. (Strength of Evidence = B)	Routine determination of plasma BNP or NT-proBNP concentration as part of a screening evaluation for structural heart disease in asymptomatic patients is not recommended. (Strength of Evidence = B)	Modification of wording and terminology
4.4	Symptoms Consistent with HF. The symptoms listed in Table 4.3 suggest the diagnosis of HF. It is recommended that each of these symptoms be solicited and graded in all patients in whom the diagnosis of HF is being considered. (Strength of Evidence = B)	Symptoms Consistent with HF. The symptoms listed in Table 4.3 suggest the diagnosis of HF. It is recommended that each of these symptoms be elicited in all patients in whom the diagnosis of HF is being considered. (Strength of Evidence = B)	Modification of wording and addition of depression to Table 4.3
4.5	Physical Examination. It is recommended that patients suspected of having HF undergo careful physical examination with determination of vital signs and be carefully evaluated for signs and symptoms shown in Table 4.4. (Strength of Evidence = C)	Physical Examination. It is recommended that patients suspected of having HF undergo careful physical examination with determination of vital signs and careful evaluation for signs shown in Table 4.4. (Strength of Evidence = B)	Modification of wording and change in Strength of Evidence from C to B and addition of reduced cardiac output and arrhythmia to cardiac abnormalities in Table 4.4
4.6	It is recommended that BNP or NT-proBNP levels be assessed in all patients suspected of having HF when the diagnosis is not certain. (Strength of Evidence = B)	It is recommended that BNP or NT-proBNP levels be assessed in all patients suspected of having HF, especially when the diagnosis is not certain. (Strength of Evidence = A)	Modification of wording and change in Strength of Evidence from B to A

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Appendix A. (*continued*)

	2006 Guideline Recommendation	2010 Guideline Recommendation	Comments
4.7	The differential diagnoses in Table 4.5 should be considered as alternative explanations for signs and symptoms consistent with HF. (Strength of Evidence = C)	Differential Diagnosis. The differential diagnoses in Table 4.5 should be considered as alternative explanations for signs and symptoms consistent with HF. (Strength of Evidence = B)	Modification of wording and change in Strength of Evidence from C to B and addition of chronic kidney disease and thyroid abnormalities to Table 4.5
4.8	No changes		
4.9	Symptoms. In addition to symptoms characteristic of HF, the following symptoms should be considered in the diagnosis of HF: • Angina • Symptoms of possible cerebral hypoperfusion, including syncope, pre-syncope, or lightheadedness • Symptoms suggestive of embolic events • Symptoms suggestive of sleep-disordered breathing (Strength of Evidence = C)	Symptoms. In addition to symptoms characteristic of HF (dyspnea, fatigue, decreased exercise tolerance, fluid retention), evaluation of the following symptoms should be considered in the diagnosis of HF: • Angina • Symptoms suggestive of embolic events • Symptoms suggestive of sleep-disordered breathing • Symptoms suggestive of arrhythmias, including palpitations • Symptoms of possible cerebral hypoperfusion, including syncope, pre-syncope, or lightheadedness (Strength of Evidence = B)	Clarification of HF symptoms and addition of arrhythmia to list of symptoms and change in Strength of Evidence from C to B
4.10	No changes		
4.11	The degree of volume excess is a key consideration during treatment. It is recommended that it be routinely assessed by determining: • Presence of paroxysmal nocturnal dyspnea or orthopnea • Daily weights and vital signs with assessment for orthostatic changes • Presence and degree of rales, S3 gallop, jugular venous pressure elevation, positive hepatojugular reflux, edema, and ascites (Strength of Evidence = B)	Volume Status. The degree of volume excess is a key consideration during treatment. It is recommended that it be routinely assessed by determining: • Presence of paroxysmal nocturnal dyspnea or orthopnea • Presence of dyspnea on exertion • Daily weights and vital signs with assessment for orthostatic changes • Presence and degree of rales, S3 gallop, jugular venous pressure elevation, hepatic enlargement and tenderness, positive hepatojugular reflux, edema, and ascites (Strength of Evidence = B)	Addition of presence of dyspnea on exertion and hepatic enlargement/tenderness to list of assessments
4.12	It is recommended that the following laboratory tests be obtained routinely in patients being evaluated for HF: serum electrolytes, blood urea nitrogen, creatinine, glucose, calcium, magnesium, lipid profile (low-density lipoprotein cholesterol, high-density lipoprotein cholesterol, triglycerides), complete blood count, serum albumin, liver function tests, urinalysis, and thyroid function. (Strength of Evidence = B)	Standard Laboratory Tests. It is recommended that the following laboratory tests be obtained routinely in patients being evaluated for HF: serum electrolytes, blood urea nitrogen, creatinine, glucose, calcium, magnesium, fasting lipid profile (low-density lipoprotein cholesterol, high-density lipoprotein cholesterol, triglycerides), complete blood count, serum albumin, uric acid, liver function tests, urinalysis, and thyroid function. (Strength of Evidence = B)	Addition of uric acid to list of standard laboratory tests
4.13	It is recommended that all patients with HF have an ECG performed to: • Assess cardiac rhythm and conduction • Detect LV hypertrophy • Evaluate QRS duration, especially when ejection fraction (EF) $<35\%$ • Detect evidence of myocardial infarction or ischemia (Strength of Evidence = B)	Electrocardiogram (ECG). It is recommended that all patients with HF have an ECG performed to: • Assess cardiac rhythm and conduction (in some cases, using Holter monitoring or event monitors) • Assess electrical dyssynchrony (wide QRS or bundle branch block), especially when left ventricular ejection fraction (LVEF) $<35\%$ • Detect LV hypertrophy or other chamber enlargement • Detect evidence of MI or ischemia • Assess QTc interval, especially with drugs that prolong QT intervals (Strength of Evidence = B)	Addition of electrical dyssynchrony and QTc interval to list of ECG assessments

4.14	It is recommended that all patients with HF have a posteroanterior and lateral chest X-ray examination for determination of heart size, evidence of fluid overload, and detection of pulmonary and other diseases. (Strength of Evidence = B)	Chest X-Ray. It is recommended that all patients with HF have a posteroanterior and lateral chest X-ray examination for determination of heart size, evidence of fluid overload, detection of pulmonary and other diseases, and appropriate placement of implanted cardiac devices. (Strength of Evidence = B)	Addition of placement of implanted cardiac devices to list of chest x-rays assessments
4.15	Additional Laboratory Tests. It is recommended that patients with no apparent etiology of HF or no specific clinical features suggesting unusual etiologies undergo additional directed blood and laboratory studies to determine the cause of HF. (Strength of Evidence = C)	Additional Laboratory Tests. It is recommended that patients with no apparent etiology of HF or no specific clinical features suggesting unusual etiologies undergo additional directed blood and laboratory studies to determine the cause of HF. (Strength of Evidence = B)	Change in Strength of Evidence from C to B
4.16		Evaluation of myocardial ischemia is recommended in those who develop new-onset LV systolic dysfunction especially in the setting of suspected myocardial ischemia or worsening symptoms with pre-existing CAD. The choice of testing modality should depend on the clinical suspicion and underlying cardiac risk factors. Coronary angiography should be considered when pre-test probability of underlying ischemic cardiomyopathy is high and an invasive coronary intervention may be considered. (See Section 13 for specific clinical situations and Strength of Evidence)	New recommendation
4.17 (previous 4.16)	Exercise testing is not recommended as part of routine evaluation in patients with HF. Specific circumstances in which maximal exercise testing with measurement of expired gases should be considered include: • Assessing disparity between symptomatic limitation and objective indicators of disease severity • Distinguishing non−HF-related causes of functional limitation, specifically cardiac versus pulmonary • Considering candidacy for cardiac transplantation or mechanical intervention • Determining the prescription for cardiac rehabilitation • Addressing specific employment capabilities Exercise testing for inducible abnormality in myocardial perfusion or wall motion abnormality should be considered to screen for the presence of coronary artery disease with inducible ischemia. (Strength of Evidence = C)	Exercise testing for functional capacity is not recommended as part of routine evaluation in patients with HF. Specific circumstances in which maximal exercise testing with measurement of expired gases should be considered include: • Assessing disparity between symptomatic limitation and objective indicators of disease severity • Distinguishing non HF-related causes of functional limitation, specifically cardiac versus pulmonary • Considering candidacy for cardiac transplantation or mechanical circulatory support • Determining the prescription for cardiac rehabilitation • Addressing specific employment capabilities (Strength of Evidence = C)	Modification of wording and deletion of recommendation for exercise testing for inducible abnormality in myocardial perfusion or wall motion abnormality
4.18 (previous 4.17)	No changes		
4.19 (previous 4.18)	It is recommended that clinical evaluation at each followup visit include the assessments listed in Table 4.9. (Strength of Evidence = B) These assessments should include the same symptoms and signs assessed during the initial evaluation. (Strength of Evidence = C)	It is recommended that clinical evaluation at each follow-up visit include determination of the elements listed in Table 4.9. (Strength of Evidence = B). These assessments should include the same symptoms and signs assessed during the initial evaluation. (Strength of Evidence = B)	Change (in second part of recommendation) Strength of Evidence from C to B

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Appendix A. (*continued*)

	2006 Guideline Recommendation	2010 Guideline Recommendation	Comments
4.20 (previous 4.19)	Routine reevaluation of cardiac function by noninvasive or invasive methods is not recommended. Repeat measurements of ventricular volume and EF should be considered under limited circumstances: • After at least 3 months of medical therapy when prophylactic ICD placement is being considered to confirm that EF criteria are still met. (Strength of Evidence = B) • In patients who show substantial clinical improvement (for example, in response to b-blocker treatment). Such change may denote improved prognosis, although it does not in itself mandate alteration or discontinuation of specific treatments. (Strength of Evidence = C) Repeat determination of EF is usually unnecessary in patients with previously documented LV dilation and low EF who manifest worsening signs or symptoms of HF. Repeat measurement should be considered when it is likely to prompt a change in patient management, such as cardiac transplantation. (Strength of Evidence = C)	In the absence of deteriorating clinical presentation, repeat measurements of ventricular volume and LVEF should be considered in these limited circumstances: • When a prophylactic implantable cardioverter defibrillator (ICD) or CRT device and defibrillator (CRT-D) placement is being considered in order to determine that LVEF criteria for device placement are still met after medical therapy (Strength of Evidence = B) • When patients show substantial clinical improvement (for example, in response to beta blocker treatment or following pregnancy in patients with peripartum cardiomyopathy). Such change may denote improved prognosis, although it does not in itself mandate alteration or discontinuation of specific treatments (see Section 7). (Strength of Evidence = C) • In alcohol and cardiotoxic substance abusers who have discontinued the abused substance. (Strength of Evidence = C) • In patients receiving cardiotoxic chemotherapy. (Strength of Evidence = B) Repeat determination of LVEF is usually unnecessary in patients with previously documented LV dilatation and low LVEF who manifest worsening signs or symptoms of HF, unless the information is needed to justify a change in patient management (such as surgery or device implantation). (Strength of Evidence = C)	Modifications of recommendation throughout
4.21 (previous 4.20)	It is recommended that reevaluation of electrolytes and renal function occur at least every 6 months in clinically stable patients and more frequently after changes in therapy or with evidence of change in volume status. More frequent assessment of electrolytes and renal function is recommended in patients with severe HF, those receiving high doses of diuretics, and those who are clinically unstable. (Strength of Evidence = C) (See Section 7 for recommendations regarding patients on angiotensin receptor blockers.)	It is recommended that reevaluation of electrolytes and renal function occur at least every 6 months in clinically stable patients and more frequently following changes in therapy or with evidence of change in volume status. More frequent assessment of electrolytes and renal function is recommended in patients with severe HF, those receiving high doses of diuretics, those on aldosterone antagonists, and those who are clinically unstable. (Strength of Evidence = C) (See Section 7 for recommendations regarding patients on angiotensin receptor blockers.)	Addition of aldosterone antagonists to list of patients in whom more frequent assessment of electrolytes and renal function is recommended.
	Section 5: Management of Asymptomatic Patients with Reduced LVEF		
5.1	It is recommended that all patients with ALVD exercise regularly according to a physician-directed prescription to avoid general deconditioning; to improve weight, blood pressure, and diabetes control; and to reduce cardiovascular risk. (Strength of Evidence = C)	It is recommended that all patients with ALVD exercise regularly according to a physician-directed prescription to avoid general deconditioning; to optimize weight, blood pressure, and diabetes control; and to reduce cardiovascular risk. (Strength of Evidence = C)	Minor wording modification
5.2	No changes		
5.3	It is recommended that alcohol consumption be discouraged in patients with ALVD. Abstinence is recommended if there is a current habit or history of excessive alcohol intake. (Strength of Evidence = C)	Alcohol abstinence is recommended if there is current or previous history of excessive alcohol intake. (Strength of Evidence = C)	Deleted phrase discouraging alcohol use in ALVD. Other minor wording modifications.
5.4	It is recommended that all patients with ALVD with hypertension have aggressive blood pressure control. (Strength of Evidence = B)	It is recommended that all patients with ALVD with hypertension achieve optimal blood pressure control. (Strength of Evidence = B)	Aggressive blood pressure control changed to optimal blood pressure control
5.5	No changes		

5.6	ARBs are recommended for asymptomatic patients with reduced LVEF who are intolerant of ACE inhibitors because of cough or angioedema. (Strength of Evidence = C) Routine use of the combination of ACE inhibitors and ARBs for prevention of HF is not recommended in this population. (Strength of Evidence = C)	ARBs are recommended for asymptomatic patients with reduced LVEF who are intolerant of ACE inhibitors from cough or angioedema. (Strength of Evidence = C) Routine use of the combination of ACE inhibitors and ARBs for prevention of HF is not recommended in this population. (Strength of Evidence = C)	Minor wording modification
5.7	It is recommended that beta blocker therapy be administered to asymptomatic patients with reduced LVEF. (Post MI, Strength of Evidence = B; non−Post MI, Strength of Evidence = C)	Beta blocker therapy should be considered in asymptomatic patients with reduced LVEF. (post-MI, Strength of Evidence = B; non post-MI, Strength of Evidence = C)	Changed from ''is recommended'' to ''should be considered''
	Section 6: Nonpharmacologic Management and Health Care Maintenance in Patients with Chronic Heart Failure		
6.1	Dietary instruction regarding sodium intake is recommended in all patients with HF. Patients with HF and diabetes, dyslipidemia, or obesity should be given specific instructions regarding carbohydrate or caloric constraints. (Strength of Evidence = B)	Dietary instruction regarding sodium intake is recommended in all patients with HF. Patients with HF and diabetes, dyslipidemia, or severe obesity should be given specific dietary instructions. (Strength of Evidence = B)	Minor wording modification
6.2	No changes		
6.3	No changes		
6.4	It is recommended that specific attention be paid to nutritional management of patients with advanced HF and unintentional weight loss or muscle wasting (cardiac cachexia). Measurement of nitrogen balance, caloric intake, and prealbumin may be useful in determining appropriate nutritional supplementation. Caloric supplementation is recommended. Anabolic steroids are not recommended for such patients. (Strength of Evidence = C)	It is recommended that specific attention be paid to nutritional management of patients with advanced HF and unintentional weight loss or muscle wasting (cardiac cachexia). Measurement of nitrogen balance, caloric intake, and prealbumin may be useful in determining appropriate nutritional supplementation. Caloric supplementation is recommended. Anabolic steroids are not recommended for cachexic patients. (Strength of Evidence = C)	Minor wording modification
6.5	No changes		
6.6	Documentation of the type and dose of nutraceutical products used by patients with HF is recommended. (Strength of Evidence = C) Nutraceutical use is not recommended for relief of symptomatic HF or for the secondary prevention of cardiovascular events. Patients should be instructed to avoid using natural or synthetic products containing ephedra (ma huang), ephedrine, or its metabolites because of an increase risk of mortality and morbidity. Products should be avoided that may have significant drug interactions with digoxin, vasodilators, beta blockers, antiarrhythmic drugs, and anticoagulants. (Strength of Evidence = B)	Documentation of the type and dose of naturoceutical products used by patients with HF is recommended. (Strength of Evidence = C) Naturoceutical use is not recommended for relief of symptomatic HF or for the secondary prevention of cardiovascular events. Patients should be instructed to avoid using natural or synthetic products containing ephedra (ma huang), ephedrine, or its metabolites because of an increased risk of mortality and morbidity. Products should be avoided that may have significant drug interactions with digoxin, vasodilators, beta blockers, antiarrhythmic drugs, and anticoagulants. (Strength of Evidence = B)	Modification of terminology (nutraceutical to naturoceutical)
6.7	No changes		
6.8	No changes		
6.9	No changes		
6.10	It is recommended that screening for endogenous or prolonged reactive depression in patients with HF be conducted after diagnosis and at periodic intervals as clinically indicated. For pharmacologic treatment, selective serotonin receptor uptake inhibitors are preferred over tricyclic antidepressants, because the latter have the potential to cause ventricular arrhythmias, but the potential for drug interactions should be considered. (Strength of Evidence = B)	It is recommended that screening for endogenous or prolonged reactive depression in patients with HF be conducted following diagnosis and at periodic intervals as clinically indicated. For pharmacologic treatment, selective serotonin reuptake inhibitors are preferred over tricyclic antidepressants, because the latter have the potential to cause ventricular arrhythmias, but the potential for drug interactions should be considered. (Strength of Evidence = B)	Minor wording modification

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	2006 Guideline Recommendation	2010 Guideline Recommendation	Comments
6.11	No changes		
6.12	No changes		
6.13	No changes		
6.14	No changes		
6.15	Endocarditis prophylaxis is not recommended based on the diagnosis of HF alone. Prophylaxis for dental and other procedures should be given according to standard clinical indications. (Strength of Evidence = C)	Endocarditis prophylaxis is not recommended based on the diagnosis of HF alone. Consistent with the AHA recommendation, 'prophylaxis should be given for only specific cardiac conditions, associated with the highest risk of adverse outcome from endocarditis.' These conditions include: 'prosthetic cardiac valves; previous infective endocarditis; congenital heart disease (CHD)' such as: 'unrepaired cyanotic CHD, including palliative shunts and conduits; completely repaired congenital heart defect with prosthetic material or device, whether placed by surgery or by catheter intervention, during the first six months after the procedure; repaired CHD with residual defects at the site or adjacent to the site of a prosthetic patch or prosthetic device (which inhibit endothelialization); cardiac transplantation recipients who develop cardiac valvulopathy.' (Strength of Evidence = C)	Addition of criteria for endocarditis prophylaxis
6.16	No changes		
6.17	No changes		
6.18	No changes		
6.19		It is recommended that patients with HF undergo exercise testing to determine suitability for exercise training (patient does not develop significant ischemia or arrhythmias). (Strength of Evidence = B) If deemed safe, exercise training should be considered for patients with HF in order to facilitate understanding of exercise expectations (heart rate ranges and appropriate levels of exercise training), to increase exercise duration and intensity in a supervised setting, and to promote adherence to a general exercise goal of 30 minutes of moderate activity/exercise, 5 days per week with warm up and cool down exercises. (Strength of Evidence = B)	New recommendation
	Section 7: Heart Failure in Patients with Reduced Ejection Fraction		
7.1	No changes		
7.2	It is recommended that other therapy be substituted for ACE inhibitors in the following circumstances: • In patients who cannot tolerate ACE inhibitors because of cough, ARBs are recommended. (Strength of Evidence = A) • The combination of hydralazine and an oral nitrate may be considered in such patients not tolerating ARB therapy. (Strength of Evidence = C) • Patients intolerant to ACE inhibitors because of hyperkalemia or renal insufficiency are likely to experience the same side effects with ARBs. In these cases, the combination of hydralazine and an oral nitrate should be considered. (Strength of Evidence = C)	It is recommended that other therapy be substituted for ACE inhibitors in the following circumstances: • In patients who cannot tolerate ACE inhibitors due to cough, ARBs are recommended. (Strength of Evidence = A) • The combination of hydralazine and an oral nitrate may be considered in such patients not tolerating ARB therapy. (Strength of Evidence = C) • Patients intolerant to ACE inhibitors from hyperkalemia or renal insufficiency are likely to experience the same side effects with ARBs. In these cases, the combination of hydralazine and an oral nitrate should be considered. (Strength of Evidence = C)	Minor wording modification

7.3 (previous 7.10)	No changes		
7.4 (previous 7.12)	ARBs should be considered in patients experiencing angioedema while on ACE inhibitors based on their underlying risk and with recognition that angioedema has been reported infrequently with these agents. (Strength of Evidence = B) The combination of hydralazine and oral nitrates may be considered in this setting for patients who do not tolerate ARB therapy. (Strength of Evidence = C)	ARBs should be considered in patients experiencing angioedema while on ACE inhibitors based on their underlying risk and with recognition that angioedema has been reported infrequently with ARBs. (Strength of Evidence = B) The combination of hydralazine and oral nitrates may be considered in this setting for patients who do not tolerate ARB therapy. (Strength of Evidence = C)	Minor wording modifications
7.5 (previous 7.11)	Individual ARBs may be considered as initial therapy rather than ACE inhibitors for patients with the following conditions: • HF post MI (Strength of Evidence = A) • Chronic HF and systolic dysfunction (Strength of Evidence = B)	Individual ARBs may be considered as initial therapy rather than ACE inhibitors for patients with the following conditions: • HF Post-MI (Strength of Evidence = A) • Chronic HF and reduced LVEF (Strength of Evidence = B)	Terminology modification (changed "systolic dysfunction" to "reduced LVEF)
7.6 (previous 7.3)	No changes		
7.7 (previous 7.4)	No changes		
7.8 (previous 7.5)	Beta blocker therapy is recommended for patients with a recent decompensation of HF after optimization of volume status and successful discontinuation of intravenous diuretics and vasoactive agents, including inotropic support. Whenever possible, beta blocker therapy should be initiated in the hospital setting at a low dose before discharge in stable patients. (Strength of Evidence = B)	Beta blocker therapy is recommended for patients with a recent decompensation of HF after optimization of volume status and successful discontinuation of intravenous diuretics and vasoactive agents, including inotropic support. Whenever possible, beta blocker therapy should be initiated in the hospital setting at a low dose prior to discharge in stable patients. (Strength of Evidence = B)	Minor wording modifications
7.9 (previous 7.6)	Beta blocker therapy is recommended in the great majority of patients with LV systolic dysfunction, even if there is concomitant diabetes, chronic obstructive lung disease, or peripheral vascular disease. Beta blocker therapy should be used with caution in patients with diabetes with recurrent hypoglycemia, asthma, or resting limb ischemia. Considerable caution should be used if beta blockers are initiated in patients with marked bradycardia (<55 beats/min) or marked hypotension (systolic blood pressure <80 mm Hg). Beta blockers are not recommended in patients with asthma with active bronchospasm. (Strength of Evidence = C)	Beta blocker therapy is recommended in the great majority of patients with HF and reduced LVEF, even if there is concomitant diabetes, chronic obstructive lung disease, or peripheral vascular disease. Beta blocker therapy should be used with caution in patients with diabetes with recurrent hypoglycemia, with asthma, or with resting limb ischemia. Considerable caution should be used if beta blockers are initiated in patients with marked bradycardia (<55 beats/min) or marked hypotension (systolic blood pressure <80 mm Hg). Beta blockers are not recommended in patients with asthma with active bronchospasm. (Strength of Evidence = C)	Modification of terminology ("LV systolic dysfunction" changed to "reduced LVEF")
7.10 (previous 7.7)	It is recommended that b-blockade be initiated at low doses and uptitrated gradually, typically no sooner than at 2-week intervals. Doses found to be effective in HF trials generally are achieved in 8 to 12 weeks. Patients developing worsening HF symptoms or other side effects during titration may require a dosage adjustment of diuretic or concomitant vasoactive medications. If side effects resolve with medication adjustment, patients can subsequently be titrated to target or maximally tolerated doses. Some patients may require a more prolonged interval during uptitration, a temporary reduction in b-blocker dose, or, in rare cases, withdrawal of therapy. (Strength of Evidence = B)	It is recommended that beta blockade be initiated at low doses and uptitrated gradually, typically at 2-week intervals in patients with reduced LVEF, and after 3-10 day intervals in patients with reduced LVEF following newly diagnosed MI. (Strength of Evidence = B)	Deleted information related to beta blocker management

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Appendix A. (*continued*)

	2006 Guideline Recommendation	2010 Guideline Recommendation	Comments
7.11 (previous 7.8)	It is recommended that beta blocker therapy be continued in most patients experiencing a symptomatic exacerbation of HF during chronic maintenance treatment. (Strength of Evidence = C) A temporary reduction of dose in this setting may be considered. Abrupt discontinuation in patients with symptomatic exacerbation should be avoided. (Strength of Evidence = C) If discontinued or reduced, beta blockers should be reinstated or the dose should be gradually increased before the patient is discharged.	It is recommended that beta blocker therapy be continued in most patients experiencing a symptomatic exacerbation of HF during chronic maintenance treatment, unless they develop cardiogenic shock, refractory volume overload, or symptomatic bradycardia (Strength of Evidence = C) A temporary reduction of dose (generally by one-half) in this setting may be considered. Abrupt discontinuation in patients with symptomatic exacerbation should be avoided, unless the situation is life-threatening. (Strength of Evidence = C) If discontinued or reduced, beta blockers should be reinstated before the patient is discharged. In general, doses should be uptitrated to the previous well-tolerated dose as soon as safely possible (Strength of Evidence =B)	Addition of criteria for beta blocker discontinuation and reinstitution
7.12 (previous 7.13)	The routine administration of an ARB is not recommended in addition to ACE inhibitor and beta blocker therapy in patients with recent acute MI and LV dysfunction. (Strength of Evidence = A)	The routine administration of an ARB is not recommended in addition to ACE inhibitor and beta blocker therapy in patients with a recent acute MI and reduced LVEF. (Strength of Evidence = A)	Modification of terminology (“LV dysfunction” changed to “reduced LVEF”)
7.13		The addition of an ARB should be considered in patients with HF due to reduced LVEF who have persistent symptoms or progressive worsening despite optimized therapy with an ACE inhibitor and beta blocker. (Strength of Evidence = A)	New recommendation
7.14	Administration of an aldosterone antagonist is recommended for patients with NYHA class IV or class III, previously class IV, HF from LV systolic dysfunction (LVEF ≤35%) while receiving standard therapy, including diuretics. (Strength of Evidence = A)	Administration of an aldosterone antagonist is recommended for patients with NYHA class IV (or class III, previously class IV) HF from reduced LVEF (<35%) while receiving standard therapy, including diuretics. (Strength of Evidence = A)	Modification of terminology (“LV systolic dysfunction” changed to “reduced LVEF”)
7.15	Administration of an aldosterone antagonist should be considered in patients after an acute MI, with clinical HF signs and symptoms and an LVEF <40%. Patients should be on standard therapy, including an ACE inhibitor (or ARB) and a b-blocker. (Strength of Evidence = A)	Administration of an aldosterone antagonist should be considered in patients following an acute MI, with clinical HF signs and symptoms or history of diabetes mellitus, and an LVEF <40%. Patients should be on standard therapy, including an ACE inhibitor (or ARB) and a beta blocker. (Strength of Evidence = A)	Addition of history of diabetes mellitus to criteria for therapy
7.16	No changes		
7.17	No changes		
7.18	No changes		
7.19	A combination of hydralazine and isosorbide dinitrate is recommended as part of standard therapy in addition to beta blockers and ACE inhibitors for African Americans with LV systolic dysfunction. • NYHA III or IV HF (Strength of Evidence = A) • NYHA II HF (Strength of Evidence = B) (See Section 15 Special Populations)	A combination of hydralazine and isosorbide dinitrate is recommended as part of standard therapy in addition to beta blockers and ACE inhibitors for African Americans with HF and reduced LVEF. • NYHA III or IV HF (Strength of Evidence = A) • NYHA II HF (Strength of Evidence = B) (See Section 15: Special Populations)	Modification of terminology (“LV systolic dysfunction” changed to “reduced LVEF”)
7.20	A combination of hydralazine and isosorbide dinitrate may be considered in non−African American patients with LV systolic dysfunction who remain symptomatic despite optimized standard therapy. (Strength of Evidence = C)	A combination of hydralazine and isosorbide dinitrate may be considered in non-African-American patients with HF and reduced LVEF who remain symptomatic despite optimized standard therapy. (Strength of Evidence = C)	Modification of terminology (“LV systolic dysfunction” changed to “reduced LVEF”)

7.21	Additional pharmacologic therapy should be considered in patients with HF due to systolic dysfunction who have persistent symptoms or progressive worsening despite optimized therapy with an ACE inhibitor and beta blocker. The choice of specific agent will be influenced by clinical considerations, including renal function status, chronic serum potassium concentration, blood pressure, and volume status. The triple combination of an ACE inhibitor, an ARB, and an aldosterone antagonist is not recommended because of the high risk of hyperkalemia. (Strength of Evidence = C) • Addition of an ARB. (Strength of Evidence = A) • Addition of an aldosterone antagonist: ○ For severe HF (Strength of Evidence = A) ○ For moderate HF (Strength of Evidence = C) • Addition of the combination of hydralazine/isosorbide dinitrate: ○ For African Americans (Strength of Evidence =A) ○ For others (Strength of Evidence = C)	Additional pharmacologic therapy should be considered in patients with HF and reduced LVEF who have persistent symptoms or progressive worsening despite optimized therapy with an ACE inhibitor and beta blocker. The choice of specific agent will be influenced by clinical considerations, including renal function status, chronic serum potassium concentration, blood pressure, and volume status. The triple combination of an ACE inhibitor, an ARB, and an aldosterone antagonist is not recommended because of the high risk of hyperkalemia. (Strength of Evidence = C) • Addition of an ARB. (Strength of Evidence = A) • Addition of an aldosterone antagonist: ○ for severe HF (Strength of Evidence =A) ○ for moderate HF (Strength of Evidence = C) ○ for post-MI HF (Strength of Evidence = A) • Addition of the combination of hydralazine/isosorbide dinitrate: ○ for African Americans (Strength of Evidence = A) ○ for others (Strength of Evidence = C)	Modification of terminology (“systolic dysfunction” changed to “reduced LVEF”); addition of post-MI HF under aldosterone antagonists
7.22	Additional pharmacological therapy should be considered in patients with HF due to systolic dysfunction who are unable to tolerate a beta blocker and have persistent symptoms or progressive worsening despite optimized therapy with an ACE inhibitor. The choice of specific agent will be influenced by clinical considerations, including renal function status, chronic serum potassium concentration, blood pressure and volume status. The triple combination of an ACE inhibitor, an ARB, and an aldosterone antagonist is not recommended due to the high risk of hyperkalemia. (Strength of Evidence = C) • Addition of an ARB. (Strength of Evidence = C) • Addition of an aldosterone antagonist: ○ for severe HF (Strength of Evidence = C) ○ for moderate HF (Strength of Evidence = C) • Addition of the combination of hydralazine/isosorbide dinitrate: ○ For African-Americans (Strength of Evidence = C) ○ for others (Strength of Evidence = C)	Additional pharmacological therapy should be considered in patients with HF and reduced LVEF *who are unable to tolerate a beta blocker* and have persistent symptoms or progressive worsening despite optimized therapy with an ACE inhibitor. The choice of specific agent will be influenced by clinical considerations, including renal function status, chronic serum potassium concentration, blood pressure and volume status. The triple combination of an ACE inhibitor, an ARB, and an aldosterone antagonist is not recommended due to the high risk of hyperkalemia. (Strength of Evidence = C) • Addition of an ARB. (Strength of Evidence = C) • Addition of an aldosterone antagonist: ○ for severe HF (Strength of Evidence = C) ○ for moderate HF (Strength of Evidence = C) • Addition of the combination of hydralazine/isosorbide dinitrate: ○ for African Americans (Strength of Evidence = C) ○ for others (Strength of Evidence = C)	Modification of terminology (“systolic dysfunction” changed to “reduced LVEF”)
7.23	No changes		
7.24	The initial dose of diuretic may be increased as necessary to relieve congestion. Restoration of normal volume status may require multiple adjustments over many days and occasionally weeks in patients with severe fluid overload evidenced by massive edema or ascites. After a diuretic effect is achieved with short acting loop diuretics, increasing administration frequency to twice or even 3 times per day will provide more diuresis with less physiologic perturbation than larger single doses. (Strength of Evidence = B) Oral torsemide may be considered in patients in whom poor absorption of oral medication or erratic diuretic effect may be present, particularly those with right-sided HF and refractory fluid retention despite high doses of other loop diuretics. (Strength of Evidence = C) Intravenous administration of diuretics may be necessary to relieve congestion. (Strength of Evidence = A) Diuretic refractoriness may represent patient noncompliance, a direct effect of diuretic use on the kidney, or progression of underlying cardiac dysfunction.	The initial dose of diuretic may be increased as necessary to relieve congestion. Restoration of normal volume status may require multiple adjustments over many days and occasionally weeks in patients with severe fluid overload evidenced by massive edema or ascites. After a diuretic effect is achieved with short-acting loop diuretics, increasing administration frequency to twice or even 3 times per day will provide more diuresis with less physiologic perturbation than larger single doses. (Strength of Evidence = B) Oral torsemide may be considered in patients in whom poor absorption of oral medication or erratic diuretic effect may be present, particularly those with right-sided HF and refractory fluid retention despite high doses of other loop diuretics. (Strength of Evidence = C) Intravenous administration of diuretics may be necessary to relieve congestion. (Strength of Evidence = A) Diuretic refractoriness may represent patient nonadherence, a direct effect of diuretic use on the kidney, or progression of underlying cardiac dysfunction.	Modification of terminology (“noncompliance” changed to “nonadherence”)

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Appendix A. (*continued*)

	2006 Guideline Recommendation	2010 Guideline Recommendation	Comments
7.25	No changes		
7.26	Careful observation for the development of side effects, including electrolyte abnormalities, symptomatic hypotension, and renal dysfunction, is recommended in patients treated with diuretics, especially when used at high doses and in combination. Patients should undergo routine laboratory studies and clinical examination as dictated by their clinical response. (Strength of Evidence = B)	Careful observation for the development of side effects, including electrolyte abnormalities, symptomatic hypotension, renal dysfunction, or worsening renal function, is recommended in patients treated with diuretics, especially when used at high doses and in combination. Patients should undergo routine laboratory studies and clinical examination as dictated by their clinical response. (Strength of Evidence = B)	Addition of worsening renal function to list of potential side effects
7.27	No changes		
7.28	No changes		
7.29	Digoxin should be considered for patients with LV systolic dysfunction (LVEF ≤40%) who have signs or symptoms of HF while receiving standard therapy, including ACE inhibitors and beta blockers: NYHA class II-III (Strength of Evidence = A) NYHA class IV (Strength of Evidence = B)	Digoxin may be considered to improve symptoms in patients with reduced LVEF (LVEF ≤40%) who have signs or symptoms of HF while receiving standard therapy, including ACE inhibitors and beta blockers: • NYHA class II-III (Strength of Evidence = B) • NYHA class IV (Strength of Evidence = C)	Modification from ''should be considered'' to ''may be considered'', and change in Strength of Evidence
7.30	It is recommended that the dose of digoxin, which should be based on lean body mass, renal function and concomitant medications, should be 0.125 mg daily in the majority of patients and the serum digoxin level should be <1.0 ng/mL. (Strength of Evidence = C)	It is recommended that the dose of digoxin, which should be based on lean body mass, renal function, and concomitant medications, should be 0.125 mg daily in the majority of patients and the serum digoxin level should be <1.0 ng/mL, generally 0.7-0.9 ng/mL. (Strength of Evidence = B)	Addition of a lower serum concentration range (0.7-0.9 ng/ml), and change in strength of evidence from C to B
7.31	Adequate control of the ventricular response to atrial fibrillation in patients with HF is recommended. (Level of Evidence = B)	Digoxin should be considered for achieving adequate control of the ventricular response to atrial fibrillation in patients with HF. (Strength of Evidence = B)	Modification from ''is recommended'' to ''should be considered''
7.32	No changes		
7.33	Treatment with warfarin (goal INR 2.0–3.0) is recommended for all patients with HF and chronic or documented paroxysmal atrial fibrillation (Strength of Evidence = A) or a history of systemic or pulmonary emboli, including stroke or transient ischemic attack, (Strength of Evidence = C) unless contraindicated.	Treatment with warfarin (goal international normalized ratio [INR] 2.0-3.0) is recommended for all patients with HF and chronic or documented paroxysmal, persistent, or long-standing atrial fibrillation (Strength of Evidence = A) or a history of systemic or pulmonary emboli, including stroke or transient ischemic attack (Strength of Evidence = C), unless contraindicated.	Addition of persistent or long-standing atrial fibrillation
7.34	No changes		
Previous 7.35			Deleted from current guideline
7.35 (previous 7.36)	Long-term treatment with an antithrombotic agent is recommended for patients with HF from ischemic cardiomyopathy, whether or not they are receiving ACE inhibitors. (Strength of Evidence = B) Aspirin is recommended in most patients for whom anticoagulation is not specifically indicated because of its proven efficacy in non-HF patients with ischemic heart disease, its convenience, and lower cost. Lower doses of aspirin (75 or 81 mg) may be preferable because data from 2 trials suggest more frequent worsening of HF at higher doses. (Strength of Evidence = C) Warfarin (goal INR 2.0–3.5) and clopidogrel (75 mg) have also prevented vascular events in post MI patients and may be considered as alternatives to aspirin. (Strength of Evidence = B)	Long-term treatment with an antiplatelet agent, generally aspirin in doses of 75 to 81 mg, is recommended for patients with HF due to ischemic cardiomyopathy, whether or not they are receiving ACE inhibitors. (Strength of Evidence = B) Warfarin (goal INR 2.0-3.0) and clopidogrel (75 mg) also have prevented vascular events in post-MI patients and may be considered as alternatives to aspirin. (Strength of Evidence = B)	Modification of terminology from ''antithrombotic'' to ''antiplatelet''; addition of recommended doses for aspirin. INR range changed to 2.0-3.0

7.36 (previous 7.37)	Routine use of aspirin is not recommended in patients with HF not from ischemic cardiomyopathy and without other evidence of atherosclerotic vascular disease. (Strength of Evidence = C)	Routine use of aspirin is not recommended in patients with HF without atherosclerotic vascular disease. (Strength of Evidence = C)	Modification of terminology
Previous 7.38			Deleted from current guideline; addressed in recommendation 7.35
7.37 (previous 7.39)	No changes		
7.38 (previous 7.40)	In patients with HF and an implantable cardioverter defibrillator (ICD), amiodarone may be considered to reduce the frequency of repetitive discharges. (Strength of Evidence = C)	In patients with HF and an ICD, amiodarone may be considered to reduce the frequency of recurrent symptomatic arrhythmias causing ICD shocks. (Strength of Evidence = C)	Modification of wording
7.39 (previous 7.41)	It is recommended that patients taking amiodarone therapy and digoxin or warfarin generally have their maintenance doses of many commonly used agents, such as digoxin, warfarin, and statins, reduced when amiodarone is initiated and then carefully monitored for the possibility of adverse drug interactions. Adjustment in doses of these drugs and laboratory assessment of drug activity or serum concentration after initiation of amiodarone is recommended. (Strength of Evidence = A)	It is recommended that when amiodarone therapy is initiated, the potential for interactions with other drugs be reviewed. The maintenance doses of digoxin, warfarin, and some statins should be reduced when amiodarone is initiated and then carefully monitored. Adjustment in doses of these drugs and laboratory assessment of drug activity or serum concentration after initiation of amiodarone is recommended. (Strength of Evidence = A)	Modification of wording
7.40		Routine use of amiodarone therapy for asymptomatic arrhythmias that are not felt to contribute to HF or ventricular dysfunction is not recommended. (Strength of Evidence = B)	New recommendation
7.41		n-3 polyunsaturated fatty acids (PUFA) may be considered to reduce mortality in HF patients with NYHA class II-IV symptoms and reduced LVEF. (Strength of Evidence = B)	New recommendation
	Section 8: Disease Management, Advance Directives, and End-of-Life Care in Heart Failure		
8.1	It is recommended that patients with HF and their family members or caregivers receive individualized education and counseling that emphasizes self-care. This education and counseling should be delivered by providers using a team approach in which nurses with expertise in HF management provide the majority of education and counseling, supplemented by physician input and, when available and needed, input from dietitians, pharmacists, and other health care providers. All HF patients benefit from education and counseling, but patients in NYHA functional class III or IV need the most intensive education, whereas patients in NYHA I or II need less intensive education. (Strength of Evidence = B) Teaching is not sufficient without skill building and specification of critical target behaviors. Essential elements of patient education to promote self-care with associated skills are shown in Table 8.1. (Strength of Evidence = B)	It is recommended that patients with HF and their family members or caregivers receive individualized education and counseling that emphasizes self-care. This education and counseling should be delivered by providers using a team approach in which nurses with expertise in HF management provide the majority of education and counseling, supplemented by physician input and, when available and needed, input from dietitians, pharmacists, and other health care providers. (Strength of Evidence = B) Teaching is not sufficient without skill building and specification of critical target behaviors. It is recommended that essential elements of patient education (with associated skills) are utilized to promote self-care as shown in Table 8.1. (Strength of Evidence = B)	Deletion of NYHA specific portion of the recommendation; modification of wording

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	2006 Guideline Recommendation	2010 Guideline Recommendation	Comments
8.2	It is recommended that patients' literacy, cognitive status, psychologic state, culture, and access to social and financial resources be taken into account for optimal education and counseling. Because cognitive impairment and depression are common in HF and can seriously interfere with learning, patients should be screened for these. Appropriate interventions, such as supportive counseling and pharmacotherapy, are recommended for those patients found to be depressed. Patients found to be cognitively impaired need additional support to manage their HF. (Strength of Evidence = C)	It is recommended that patients' literacy, cognitive status, psychological state, culture, and access to social and financial resources be taken into account for optimal education and counseling. Because cognitive impairment and depression are common in HF and can seriously interfere with learning, patients should be screened for these. Patients found to be cognitively impaired need additional support to manage their HF. (Strength of Evidence = B)	Deletion of description of interventions; modification of Strength of Evidence from C to B
8.3	No changes		
8.4	It is recommended that the frequency and intensity of patient education and counseling vary according to the stage of illness. Patients in advanced HF or with persistent difficulty adhering to the recommended regimen require the most eduction and counseling. Patients should be offered a variety of options for learning about HF according to their individual preferences: videotape, one-on-one or group discussion, reading materials, translators, telephone calls, mailed information, internet, visits. Repeated exposure to material is essential because a single session is never sufficient. (Strength of Evidence = B)	It is recommended that the frequency and intensity of patient education and counseling vary according to the stage of the illness. Patients in advanced HF or persistent difficulty adhering to the recommended regimen require the most education and counseling. Patients should be offered a variety of options for learning about HF according to their individual preferences: videotape, one-on-one or group discussion, reading materials, translators, telephone calls, mailed information, internet, visits. Repeated exposure to material is recommended because a single session is never sufficient. (Strength of Evidence = B)	Modification of wording
8.5	No changes		
8.6	No changes		
8.7	Patients recently hospitalized for HF and other patients at high risk should be considered for referral to a comprehensive HF disease management program that delivers individualized care. High-risk patients include those with renal insufficiency, low output state, diabetes, chronic obstructive pulmonary disease, persistent NYHA class III or IV symptoms, frequent hospitalization for any cause, multiple active comorbidities, or a history of depression, cognitive impairment, or persistent nonadherence to therapeutic regimens. (Strength of Evidence = A)	Patients recently hospitalized for HF and other patients at high risk for HF decompensation should be considered for comprehensive HF disease management. High-risk patients include those with renal insufficiency, low output state, diabetes, chronic obstructive pulmonary disease, persistent NYHA class III or IV symptoms, frequent hospitalization for any cause, multiple active comorbidities, or a history of depression, cognitive impairment, inadequate social support, poor health literacy, or persistent nonadherence to therapeutic regimens. (Strength of Evidence = A)	Addition of poor health literacy
8.8	No changes		
8.9	No changes		
8.10	No changes		
8.11	Patient and family or caregiver discussions about quality of life and prognosis are recommended as part of the disease management of HF. (Strength of Evidence = C)	It is recommended that patient and family or caregiver discussions about quality of life and prognosis be included in the disease management of HF. (Strength of Evidence = C)	Modification of wording

8.12	It is recommended that the patient's status be optimized medically and psychologically before discussing the possibility that end-of-life care is indicated. The decision to declare a patient as an appropriate candidate for end-of-life care should be made by physicians experienced in the care of patients with HF. End-of-life management should be coordinated with the patient's primary care physician. As often as possible, discussions regarding end-of-life care should be initiated while the patient is still capable of participating in decision making. (Strength of Evidence = C)	It is recommended that • Seriously ill patients with HF and their families be educated to understand that patients with HF are at high risk of death, even while aggressive efforts are made to prolong life. • Patients with HF be made aware that HF is potentially life-limiting, but that pharmacologic and device therapies and self-management can prolong life. In most cases, chronic HF pharmacologic and device therapies should be optimized as indicated before identifying that patients are near end-of-life. • Identification of end-of-life in a patient should be made in collaboration with clinicians experienced in the care of patients with HF when possible. • End-of-life management should be coordinated with the patient's primary care physician. • As often as possible, discussions regarding end-of-life care should be initiated while the patient is still capable of participating in decision-making. (Strength of Evidence = C)	Addition of criteria for end of life care
8.13	End-of-life care should be considered in patients who have advanced, persistent HF with symptoms at rest despite repeated attempts to optimize pharmacologic and nonpharmacologic therapy, as evidenced by one or more of the following: • Frequent hospitalizations (3 or more per year) • Chronic poor quality of life with inability to accomplish activities of daily living • Need for intermittent or continuous intravenous support • Consideration of assist devices as destination therapy (Strength of Evidence = C)	End-of-life care should be considered in patients who have advanced, persistent HF with symptoms at rest despite repeated attempts to optimize pharmacologic, cardiac device, and other therapies, as evidenced by 1 or more of the following: • HF hospitalization (Strength of Evidence = B) • Chronic poor quality of life with minimal or no ability to accomplish activities of daily living (Strength of Evidence = C) • Need for continuous intravenous inotropic therapy support (Strength of Evidence = B)	Addition of cardiac device to list of optimization therapies; modification of strength of evidence
8.14	It is recommended that end-of-life care strategies be individualized, include effective symptom management, and avoid unnecessary testing and interventions. (Strength of Evidence = C)	It is recommended that end-of-life care strategies be individualized and include core HF pharmacologic therapies, effective symptom management and comfort measures, while avoiding unnecessary testing. New life-prolonging interventions should be discussed with patients and care-givers with careful discussion of whether they are likely to improve symptoms. (Strength of Evidence = C)	Addition of information regarding end-of-life care strategies
8.15	It is recommended that, as part of end-of life-care, patients and their families/caregivers be given specific directions concerning their response to clinical events if they decide against resuscitation. Inactivation of an implantable defibrillation device should be discussed. (Strength of Evidence = C)	It is recommended that a specific discussion about resuscitation be held in the context of planning for overall care and for emergencies with all patients with HF. The possibility of SCD for patients with HF should be acknowledged. Specific plans to reduce SCD (for example with an ICD) or to allow natural death should be based on the individual patient's risks and preferences for an attempt at resuscitation with specific discussion of risks and benefits of inactivation the ICD. Preferences for attempts at resuscitation and plans for approach to care should be readdressed at turning points in the patient's course or if potentially life-prolonging interventions are considered. (Strength of Evidence = C)	Addition of information regarding resuscitation
8.16		It is recommended that, as part of end-of-life care, patients and their families/caregivers have a plan to manage a sudden decompensation, death, or progressive decline. Inactivation of an implantable defibrillation device should be discussed in the context of allowing natural death at end of life. A process for deactivating defibrillators should be clarified in all settings in which patients with HF receive care. (Strength of Evidence = C)	New recommendation

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	2006 Guideline Recommendation	2010 Guideline Recommendation	Comments
8.17	Patients with HF undergoing end-of-life care may be considered for hospice services that can be delivered in the home, a hospital setting, or a special hospice unit. (Strength of Evidence = C)	Patients with HF receiving end-of-life care should be considered for enrollment in hospice that can be delivered in the home, a nursing home, or a special hospice unit. (Strength of Evidence = C)	Modification from "may be considered" to "should be considered"
Previous 8.16 and 8.18			Deleted recommendations; portions of these recommendations have been incorporated into recommendations 8.15 and 8.16
	Section 9: Electrophysiology Testing and the Use of Devices in Heart Failure		
9.1	It is recommended that the decision to undertake electrophysiologic intervention be made in light of functional status and prognosis based on severity of underlying HF and comorbid conditions. If LV dysfunction is a reason for recommending electrophysiologic intervention, LV function should be re-assessed, ideally after 3–6 months of optimal medical therapy. (Strength of Evidence = C)	It is recommended that the decision to undertake electrophysiologic intervention, including ICD implantation, be made in light of functional status and prognosis based on severity of underlying HF and comorbid conditions. If an ICD is considered due to LV dysfunction which is of recent onset, LV function should be reassessed, ideally after 3-6 months of optimal medical therapy. (Strength of Evidence = C)	Modification/clarification of wording
9.2	Immediate evaluation is recommended in patients with HF who present with syncope. In the absence of a clear identifiable noncardiac cause, patients should be referred for electrophysiologic evaluation. (Strength of Evidence = C)	Immediate evaluation is recommended in patients with HF who present with syncope. In the absence of a clear identifiable noncardiac cause, consultation with an EP specialist should be obtained. (Strength of Evidence = C)	Modification/clarification of wording
9.3	No changes		
9.4	In patients with or without concomitant coronary artery disease (including a prior MI >1 month ago): a) Prophylactic ICD placement should be considered (LVEF ≤30%) and may be considered (LVEF 31–35%) for those with mild to moderate HF symptoms (NYHA II-III). (Strength of Evidence = A) See Recommendation 9.1 for additional criteria. b) Concomitant ICD placement should be considered in patients undergoing implantation of a biventricular pacing device according to the criteria in Recommendations 9.7–9.8. (Strength of Evidence = B) See Recommendation 9.1 for additional criteria.	a. Prophylactic ICD placement should be considered in patients with an LVEF ≤35% and mild to moderate HF symptoms: • Ischemic etiology (Strength of Evidence = A) • Non-ischemic etiology (Strength of Evidence = B) See Recommendation 9.1 for additional criteria. b. In patients who are undergoing implantation of a biventricular pacing device according to the criteria in recommendations 9.7-9.8, use of a device that provides defibrillation should be considered. (Strength of Evidence = B) See Recommendation 9.1 for additional criteria.	Revision of LVEF criteria and strength of evidence based on etiology
9.5	ICD placement is not recommended in chronic, severe refractory HF when there is no reasonable expectation for improvement. (Strength of Evidence = C)	ICD placement is not recommended in chronic, severe refractory HF when there is no reasonable expectation for improvement or in patients with a life expectancy of less than 1 year. (Strength of Evidence = C)	Addition of life expectancy criterion to recommendation
9.6	ICD implantation is recommended for survivors of cardiac arrest from ventricular fibrillation or hemodynamically unstable sustained ventricular tachycardia without evidence of acute MI or if the event occurs more than 48 hours after the onset of infarction in the absence of a recurrent ischemic event. (Strength of Evidence = A)	ICD implantation is recommended for survivors of cardiac arrest from ventricular fibrillation or hemodynamically unstable sustained VT that is not due to a transient, potentially reversible cause, such as acute MI. (Strength of Evidence = A)	Revision of MI criteria
9.7	Biventricular pacing therapy should be considered for patients with sinus rhythm, a widened QRS interval (≥120 ms) and severe LV systolic dysfunction (LVEF ≤35% with LV dilatation >5.5 cm) who have persistent, moderate to severe HF (NYHA III) despite optimal medical therapy. (Strength of Evidence = A)	Biventricular pacing therapy is recommended for patients in sinus rhythm with a widened QRS interval (≥120 ms) and severe LV systolic dysfunction LVEF (≤ 35%) who have persistent, moderate to severe HF (NYHA III) despite optimal medical therapy. (Strength of Evidence = A)	Modification from "should be considered" to "is recommended"; removal of LV dimension criterion

9.8		Biventricular pacing therapy may be considered for patients with atrial fibrillation with a widened QRS interval (≥120 ms) and severe LV systolic dysfunction LVEF ≤35% who have persistent, moderate to severe HF (NYHA III) despite optimal medical therapy. (Strength of Evidence = B)	New recommendation
9.9 (Previous 9.8)	Selected ambulatory NYHA IV patients may be considered for biventricular pacing therapy. (Strength of Evidence = B)	Selected ambulatory NYHA IV patients in sinus rhythm with QRS ≥ 120 ms and LV systolic dysfunction may be considered for biventricular pacing therapy. (Strength of Evidence = B)	Additional criteria for patient selection
9.10 (previous 9.9)	Biventricular pacing therapy is not recommended in patients who are asymptomatic or have mild HF symptoms. (Strength of Evidence = C)	Biventricular pacing therapy may be considered in patients with reduced LVEF and QRS ≥ 150 ms who have NYHA I or II HF symptoms. (Strength of Evidence = B)	Modification from ''is not recommended'' to ''may be considered''; modification of strength of evidence from C to B; additional criteria for patient selection
9.11		In patients with reduced LVEF who require chronic pacing and in whom frequent ventricular pacing is expected, biventricular pacing may be considered. (Strength of Evidence = C)	New recommendation
9.12 (previous 9.10)	No changes		
	Section 10: Surgical Approaches to the Treatment of Heart Failure		
10.1	No changes		
10.2	No changes		
10.3	No changes		
10.4	No changes		
10.5	No changes		
10.6	No changes		
10.7		Patients with refractory HF and hemodynamic instability, and/or compromised end-organ function, with relative contraindications to cardiac transplantation or permanent mechanical circulatory assistance expected to improve with time or restoration of an improved hemodynamic profile should be considered for urgent mechanical circulatory support as a ''bridge to decision.'' These patients should be referred to a center with expertise in the management of patients with advanced HF. (Strength of Evidence = C)	New recommendation
	Section 11: Evaluation and Management of Patients with Heart Failure and Preserved LVEF		
11.1	Careful attention to differential diagnosis is recommended in patients with HF and preserved LVEF to distinguish among a variety of cardiac disorders, because treatments may differ. These various entities may be distinguished based on echocardiography, electrocardiography, and stress imaging (via exercise or pharmacologic means using myocardial perfusion or echocardiographic imaging). See algorithm in Figure 11.1 for a detailed approach to differential diagnosis. (Strength of Evidence = C)	Careful attention to differential diagnosis is recommended in patients with HF and preserved LVEF to distinguish among a variety of cardiac disorders, because treatments may differ. These various entities may be distinguished based on echocardiography, electrocardiography, and stress imaging (via exercise or pharmacologic means, using myocardial perfusion or echocardiographic imaging) and cardiac catheterization. See Figures 11.1, 11.2, and 11.3 for guidance to a differential diagnosis. (Strength of Evidence = C)	Addition of cardiac catheterization to list of diagnostic tools, modification of Figure 11.3 and addition of Figures 11.1 and 11.2.

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	2006 Guideline Recommendation	2010 Guideline Recommendation	Comments
11.2	Evaluation for the possibility of ischemic heart disease and inducible myocardial ischemia is recommended in patients with HF and preserved LVEF. (Strength of Evidence = C)	Evaluation for ischemic heart disease and inducible myocardial ischemia is recommended in patients with HF and preserved LVEF (see Section 13). (Strength of Evidence = C)	Minor wording modifications
11.3	Aggressive blood pressure management is recommended in patients with HF and preserved LVEF (Section 14, Recommendation 14.15). (Strength of Evidence = C)	Blood pressure monitoring is recommended in patients with HF and preserved LVEF (Section 14, Recommendation 14.1). (Strength of Evidence = C)	Modification of terminology (''aggressive blood pressure management'' changed to ''blood pressure monitoring'')
11.4	No changes		
11.5	No changes		
11.6	ARBs or ACE inhibitors should be considered in patients with HF and preserved LVEF. (Strength of evidence = B) • ARBs (Strength of Evidence = B) • ACE inhibitors (Strength of Evidence = C)	In the absence of other specific indications for these drugs, ARBs or ACE inhibitors may be considered in patients with HF and preserved LVEF. • ARBs (Strength of Evidence = C) • ACE inhibitors (Strength of Evidence = C)	Modification from ''should be considered'' to ''may be considered''; modification of strength of evidence for ARBs from B to C
11.7	No changes		
11.8	No changes		
11.9	Calcium channel blockers should be considered in patients with: • Atrial fibrillation requiring control of ventricular rate in whom b-blockers have proven inadequate for this purpose because of intolerance. In these patients, diltiazem or verapamil should be considered. (Strength of Evidence = C) • Symptom-limiting angina. (Strength of Evidence = A) • Hypertension. Amlodipine should be considered. (Strength of Evidence = C)	Calcium channel blockers should be considered in patients with HF and preserved LVEF and: • Atrial fibrillation requiring control of ventricular rate and intolerance to beta blockers. In these patients, diltiazem or verapamil should be considered. (Strength of Evidence = C) • Symptom-limiting angina. (Strength of Evidence = A) • Hypertension. (Strength of Evidence = C)	Modification of wording regarding beta blocker intolerance
11.10	Measures to restore and maintain sinus rhythm should be considered in patients who have symptomatic atrial flutter-fibrillation, but this decision should be individualized. (Strength of Evidence = C)	Measures to restore and maintain sinus rhythm may be considered in patients who have symptomatic atrial flutter-fibrillation and preserved LVEF, but this decision should be individualized. (Strength of Evidence = C)	Modification from ''should be considered'' to ''may be considered''
	Section 12: Evaluation and Management of Patients with Acute Decompensated Heart Failure		
12.1	The diagnosis of decompensated HF should be based primarily on signs and symptoms. (Strength of Evidence = C) When the diagnosis is uncertain, determination of BNP or NT-proBNP concentration should be considered in patients being evaluated for dyspnea who have signs and symptoms compatible with HF. (Strength of Evidence = A) 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.	The diagnosis of ADHF should be based primarily on signs and symptoms. (Strength of Evidence = C) When the diagnosis is uncertain, determination of BNP or NT-proBNP concentration is recommended in patients being evaluated for dyspnea who have signs and symptoms compatible with HF. (Strength of Evidence = A) 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, and with the knowledge of cardiac and non-cardiac factors that can raise or lower natriuretic peptide levels.	Modification of BNP recommendation from ''should be considered'' to ''is recommended''
12.2	No changes		

12.3	No changes		
12.4	No changes		
12.5	No changes		
12.6	It is recommended that diuretics be administered at doses needed to produce a rate of diuresis sufficient to achieve optimal volume status with relief of signs and symptoms of congestion (edema, elevated JVP, dyspnea), without inducing an excessively rapid reduction in intravascular volume, which may result in symptomatic hypotension and/or worsening renal function. (Strength of Evidence = C)	It is recommended that diuretics be administered at doses needed to produce a rate of diuresis sufficient to achieve optimal volume status with relief of signs and symptoms of congestion (edema, elevated JVP, dyspnea), without inducing an excessively rapid reduction in 1) intravascular volume, which may result in symptomatic hypotension and/or worsening renal function, or 2) serum electrolytes, which may precipitate arrhythmias or muscle cramps. (Strength of Evidence = C)	Addition of serum electrolytes
12.7	No changes		
12.8	Monitoring of daily weights, intake, and output is recommended to assess clinical efficacy of diuretic therapy. Routine use of a Foley catheter is not recommended for monitoring volume status. However, placement of a catheter is recommended when close monitoring of urine output is needed. (Strength of Evidence = C)	Monitoring of daily weights, intake, and output is recommended to assess clinical efficacy of diuretic therapy. Routine use of a Foley catheter is not recommended for monitoring volume status. However, placement of a catheter is recommended when close monitoring of urine output is needed or if a bladder outlet obstruction is suspected of contributing to worsening renal function. (Strength of Evidence = C)	Addition of criterion for catheter placement
12.9	Careful observation for development of a variety of side effects, including renal dysfunction, electrolyte abnormalities and symptomatic hypotension, is recommended in patients treated with diuretics, especially when used at high doses and in combination. Patients should undergo routine laboratory studies and clinical examination as dictated by their clinical response. (Strength of Evidence = C) Serum potassium and magnesium levels should be monitored at least daily and maintained in the normal range. More frequent monitoring may be necessary when diuresis is rapid. (Strength of Evidence = C) Overly rapid diuresis may be associated with severe muscle cramps, which should be treated with potassium replacement if indicated. (Strength of Evidence = C)	Careful observation for development of a variety of side effects, including renal dysfunction, electrolyte abnormalities, symptomatic hypotension, and gout is recommended in patients treated with diuretics, especially when used at high doses and in combination. Patients should undergo routine laboratory studies and clinical examination as dictated by their clinical response. (Strength of Evidence = C) It is recommended that serum potassium and magnesium levels should be monitored at least daily and maintained in the normal range. More frequent monitoring may be necessary when diuresis is rapid. (Strength of Evidence = C) Overly rapid diuresis may be associated with severe muscle cramps. If indicated, treatment with potassium replacement is recommended. (Strength of Evidence = C)	Addition of gout as side effect Wording modified
12.10	No changes		
12.11	When congestion fails to improve in response to diuretic therapy, the following options should be considered: • Sodium and fluid restriction, • Increased doses of loop diuretic, • Continuous infusion of a loop diuretic, or • Addition of a second type of diuretic orally (metolazone or spironolactone) or intravenously (chlorothiazide). • A fifth option, ultrafiltration, may be considered. (Strength of Evidence = C)	When congestion fails to improve in response to diuretic therapy, the following options should be considered: • Re-evaluating presence/absence of congestion • Sodium and fluid restriction, • Increasing doses of loop diuretic, • Continuous infusion of a loop diuretic, or • Addition of a second type of diuretic orally (metolazone or spironolactone) or intravenously (chlorothiazide). Another option, ultrafiltration, may be considered. (Strength of Evidence = C)	Addition of re-evaluation of congestion
12.12	A low-sodium diet (2 g daily) is recommended, as is supplemental oxygen, as needed for hypoxemia. (Strength of Evidence = C) In patients with recurrent or refractory volume overload, stricter sodium restriction may be considered. (Strength of Evidence = C)	A low sodium diet (2 g daily) is recommended for most hospitalized patients. (Strength of Evidence = C) In patients with recurrent or refractory volume overload, stricter sodium restriction may be considered. (Strength of Evidence = C)	Deletion of supplemental oxygen (moved to recommendation 12.14)

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Appendix A. (*continued*)

	2006 Guideline Recommendation	2010 Guideline Recommendation	Comments
12.13	No changes		
12.14	Routine administration of supplemental oxygen in the absence of hypoxia is not recommended. (Strength of Evidence = C)	Routine administration of supplemental oxygen in the presence of hypoxia is recommended. (Strength of Evidence = C) Routine administration of supplemental oxygen in the absence of hypoxia is not recommended. (Strength of Evidence = C)	Addition of recommendation for oxygen in the presence of hypoxemia
12.15		Use of non-invasive positive pressure ventilation may be considered for severely dyspneic patients with clinical evidence of pulmonary edema. (Strength of Evidence = A)	New recommendation
12.16		Venous thromboembolism prophylaxis with low dose unfractionated heparin, low molecular weight heparin, or fondaparinux to prevent proximal deep venous thrombosis and pulmonary embolism is recommended for patients who are admitted to the hospital with ADHF and who are not already anticoagulated and have no contraindication to anticoagulation. (Strength of Evidence = B) Venous thromboembolism prophylaxis with a mechanical device (intermittent pneumatic compression devices or graded compression stockings) to prevent proximal deep venous thrombosis and pulmonary embolism should be considered for patients who are admitted to the hospital with ADHF and who are not already anticoagulated and who have a contraindication to anticoagulation. (Strength of Evidence = C)	New recommendation
12.17 (previous 12.15)	In the absence symptomatic hypotension, intravenous nitroglycerin, nitroprusside, or nesiritide may be considered as an addition to diuretic therapy for rapid improvement of congestive symptoms in patients admitted with ADHF. Frequent blood pressure monitoring is recommended with these agents. (Strength of Evidence = B). These agents should be decreased in dosage on discontinued if symptomatic hypotension develops. (Strength of Evidence = B) Reintroduction in increasing doses may be considered once symptomatic hypotension is resolved. (Strength of Evidence = C)	In the absence of symptomatic hypotension, intravenous nitroglycerin, nitroprusside or nesiritide may be considered as an addition to diuretic therapy for rapid improvement of congestive symptoms in patients admitted with ADHF. (Strength of Evidence = B) Frequent blood pressure monitoring is recommended with these agents. (Strength of Evidence = B) These agents should be decreased in dosage or discontinued if symptomatic hypotension or worsening renal function develops. (Strength of Evidence = B) Reintroduction in increasing doses may be considered once symptomatic hypotension is resolved. (Strength of Evidence = C)	Addition of worsening renal function as potential side effect
12.18 (previous 12.16)	No changes		
12.19 (previous 12.17)	Intravenous vasodilators (nitroprusside, nitroglycerin, or nesiritide) may be considered in patients with ADHF and advanced HF who have persistent severe HF despite aggressive treatment with diuretics and standard oral therapies. (Strength of Evidence = C)	Intravenous vasodilators (nitroprusside, nitroglycerin, or nesiritide) may be considered in patients with ADHF who have persistent severe HF despite aggressive treatment with diuretics and standard oral therapies. • Nitroprusside (Strength of Evidence = B) • Nitroglycerine, Nesiritide (Strength of Evidence = C)	Modification of strength of evidence for nitroprusside from C to B

12.20 (previous 12.18)	Intravenous inotropes (milrinone or dobutamine) may be considered to relieve symptoms and improve end-organ function in patients with advanced HF characterized by LV dilation, reduced LVEF, and diminished peripheral perfusion or end-organ dysfunction (low output syndrome), particularly if these patients have marginal systolic blood pressure (<90 mm Hg), have symptomatic hypotension despite adequate filling pressure, or are unresponsive to, or intolerant of, intravenous vasodilators. (Strength of Evidence = C) These agents may be considered in similar patients with evidence of fluid overload if they respond poorly to intravenous diuretics or manifest diminished or worsening renal function. (Strength of Evidence = C) When adjunctive therapy is needed in other patients with ADHF, administration of vasodilators should be considered instead of intravenous inotropes (milrinone or dobutamine). (Strength of Evidence = B) Intravenous inotropes (milrinone or dobutamine) are not recommended unless left heart filling pressures are known to be elevated based on direct measurement or clear clinical signs. (Strength of Evidence = B) Administration of intravenous inotropes (milrinone or dobutamine) in the setting of ADHF should be accompanied by continuous or frequent blood pressure monitoring and continuous monitoring of cardiac rhythm. (Strength of Evidence = C) If symptomatic hypotension or worsening tachyarrhythmias develop during administration of these agents, discontinuation or dose reduction should be considered. (Strength of Evidence = C)	Intravenous inotropes (milrinone or dobutamine) may be considered to relieve symptoms and improve end-organ function in patients with advanced HF characterized by LV dilation, reduced LVEF, and diminished peripheral perfusion or end-organ dysfunction (low output syndrome), particularly if these patients have marginal systolic blood pressure (< 90 mm Hg), have symptomatic hypotension despite adequate filling pressure, or are unresponsive to, or intolerant of, intravenous vasodilators. (Strength of Evidence = C) These agents may be considered in similar patients with evidence of fluid overload if they respond poorly to intravenous diuretics or manifest diminished or worsening renal function. (Strength of Evidence = C) When adjunctive therapy is needed in other patients with ADHF, administration of vasodilators should be considered instead of intravenous inotropes (milrinone or dobutamine). (Strength of Evidence = C) Intravenous inotropes (milrinone or dobutamine) are not recommended unless left heart filling pressures are known to be elevated or cardiac index is severely impaired based on direct measurement or clear clinical signs. (Strength of Evidence = C) It is recommended that administration of intravenous inotropes (milrinone or dobutamine) in the setting of ADHF be accompanied by continuous or frequent blood pressure monitoring and continuous monitoring of cardiac rhythm. (Strength of Evidence = C) If symptomatic hypotension or worsening tachyarrhythmias develop during administration of these agents, discontinuation or dose reduction should be considered. (Strength of Evidence = C)	Modification of strength of evidence from B to C for portions of this recommendation Wording modified
12.21 (previous 12.19)	No changes		
12.22 (previous 12.20)	Invasive hemodynamic monitoring should be considered in a patient: Who is refractory to initial therapy, Whose volume status and cardiac filling pressures are unclear, Who has clinically significant hypotension (typically systolic blood pressure <80 mm Hg) or worsening renal function during therapy, or In whom documentation of an adequate hemodynamic response to the inotropic agent is necessary when chronic outpatient infusion is being considered. (Strength of Evidence = C)	Invasive hemodynamic monitoring should be considered in a patient: • who is refractory to initial therapy, • whose volume status and cardiac filling pressures are unclear, • who has clinically significant hypotension (typically SBP < 80mm Hg) or worsening renal function during therapy, or • who is being considered for cardiac transplant and needs assessment of degree and reversibility of pulmonary hypertension, or • in whom documentation of an adequate hemodynamic response to the inotropic agent is necessary when chronic outpatient infusion is being considered. (Strength of Evidence = C)	Addition of cardiac transplant as criterion for invasive hemodynamic monitoring
12.23 (previous 12.21)	No changes		
12.24 (previous 12.22)	It is recommended that every effort be made to use the hospital stay for assessment and improvement of patient compliance via patient and family education and social support services (Section 8). (Strength of Evidence = C)	It is recommended that every effort be made to use the hospital stay for assessment and improvement of patient adherence via patient and family education and social support services (see Section 8). (Strength of Evidence = B)	Modification of strength of evidence from C to B; change in terminology (“compliance” to “adherence”)

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Appendix A. (*continued*)

	2006 Guideline Recommendation	2010 Guideline Recommendation	Comments
12.25 (previous 12.23)	No changes		
12.26 (previous 12.24)	Discharge planning is recommended as part of the management of patients with ADHF. Discharge planning should address the following issues: • Details regarding medication, dietary sodium restriction, and recommended activity level • Follow-up by phone or clinic visit early after discharge to reassess volume status • Medication and dietary compliance • Monitoring of body weight, electrolytes, and renal function • Consideration of referral for formal disease management (Strength of Evidence = C)	Discharge planning is recommended as part of the management of patients with ADHF. Discharge planning should address the following issues: • Details regarding medication, dietary sodium restriction, and recommended activity level • Follow-up by phone or clinic visit early after discharge to reassess volume status • Medication and dietary compliance • Alcohol moderation and smoking cessation • Monitoring of body weight, electrolytes and renal function • Consideration of referral for formal disease management (Strength of Evidence = C)	Addition of alcohol moderation and smoking cessation
	Section 13: Evaluation and Therapy for Heart Failure in the Setting of Ischemic Heart Disease		
13.1	Assessment for risk factors for CAD is recommended in all patients with chronic HF regardless of EF. (Strength of Evidence = A) The diagnostic approach for CAD should be individualized based on patient preference and comorbidities, eligibility and willingness to perform revascularization. (Strength of Evidence = C)	Ongoing assessment for risk factors for CAD is recommended in all patients with chronic HF regardless of LVEF. (Strength of Evidence = A)	Moved diagnostic portion of recommendation to 13.2
13.2		It is recommended that the diagnostic approach for CAD be individualized based on patient preference and comorbidities, eligibility, symptoms suggestive of angina and willingness to undergo revascularization. (Strength of Evidence = C)	Previously part of 13.1
13.3 (previous 13.2)	It is recommended that patients with HF and angina undergo cardiac catheterization with coronary angiography to assess for potential revascularization. (Strength of Evidence = B)	It is recommended that patients with HF and symptoms suggestive of angina undergo cardiac catheterization with coronary angiography to assess for potential revascularization. (Strength of Evidence = B)	Modification of wording
13.4 (previous 13.3)	It is recommended that patients with HF, no angina, and known CAD should undergo noninvasive stress imaging and/or coronary angiography to assess severity of coronary disease and the presence of ischemia. (Strength of Evidence = C)	It is recommended that, at the initial diagnosis of HF and any time symptoms worsen without obvious cause, patients with HF, no angina, and known CAD should undergo risk assessment that may include noninvasive stress imaging and/or coronary angiography to assess severity of coronary disease and the presence of ischemia. (Strength of Evidence = C)	Clarification of type and timing of risk assessments
13.5 (previous 13.4)	No changes		
13.6 (previous 13.5)	No changes		

13.7 (previous 13.6)	Any of the following imaging tests may be used to identify inducible ischemia or viable but nocontractile myocardium: • Exercise or pharmacologic stress myocardial perfusion imaging • Exercise or pharmacologic stress echocardiography • Cardiac magnetic resonance imaging • Positron emission tomography scanning (Strength of Evidence = B)	Any of the following imaging tests should be considered to identify inducible ischemia or viable myocardium: • Exercise or pharmacologic stress myocardial perfusion imaging • Exercise or pharmacologic stress echocardiography • Cardiac magnetic resonance imaging • Positron emission tomography scanning (Strength of Evidence = B)	Modification of wording
13.8 (previous 13.7)	No changes		
13.9 (previous 13.8)	Antiplatelet therapy is recommended in patients with HF and CAD unless contraindicated. (Aspirin, Strength of Evidence = B; Clopidogrel, Strength of Evidence = C)	Antiplatelet therapy is recommended to reduce vascular events in patients with HF and CAD unless contraindicated. (aspirin, Strength of Evidence = A; clopidogrel, Strength of Evidence = B)	Addition of indication for antiplatelet therapy, and modification of strength of evidence
13.10 (previous 13.9)	ACE inhibitors are recommended in all patients with systolic dysfunction or preserved systolic function after an MI. (Strength of Evidence = A)	ACE inhibitors are recommended in all patients with either reduced or preserved LVEF after an MI. (Strength of Evidence = A)	Modification of terminology (“systolic dysfunction” changed to “reduced LVEF”)
13.11 (previous 13.10)	No changes		
13.12 (previous 13.11)	It is recommended that ACE-inhibitor and beta blocker therapy be initiated early (<48 hours) during hospitalization in hemodynamically stable post MI patients with LV dysfunction or HF. (Strength of Evidence = A)	It is recommended that ACE-inhibitor and beta blocker therapy be initiated early (<48 hours) during hospitalization in hemodynamically stable post-MI patients with reduced LVEF or HF. (Strength of Evidence = A)	Modification of terminology (“LV dysfunction” changed to “reduced LVEF”)
13.13 (previous 13.12)	No changes		
13.14 (previous 13.13)	Calcium channel blockers should be considered in patients with HF who have angina despite the optimal use of beta blockers and nitrates. Amlodipine and felodipine are the preferred calcium channel blockers in patients with angina and decreased systolic function. (Strength of Evidence = C)	Calcium channel blockers may be considered in patients with HF who have angina despite the optimal use of beta blockers and nitrates. Amlodipine and felodipine are the preferred calcium channel blockers in patients with angina and decreased systolic function. Based on available data, first generation calcium channel blockers (i.e. diltiazem, verapamil) should be avoided in patients with CAD, HF, and LVEF <40, unless necessary for heart rate control or other indications. (Strength of Evidence = C)	Addition of calcium channel blockers that should be avoided
13.15 (previous 13.14)	No changes		
13.16 (previous 13.15)	No changes		
	Section 14: Managing Patients with Hypertension and Heart Failure		
14.1	It is recommended that blood pressure be aggressively treated to lower systolic and usually diastolic levels. Target resting levels should be <130/<80 mm Hg, if tolerated. (Strength of Evidence = C)	It is recommended that blood pressure be optimally treated to lower systolic and usually diastolic levels. More than 1 drug may be required. Target resting levels should be <130/<80 mm Hg, if tolerated. (Strength of Evidence = A)	Modification of wording and change in strength of evidence from C to A

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	2006 Guideline Recommendation	2010 Guideline Recommendation	Comments
Previous 14.2			Deleted
14.2 (previous 14.3)	No changes		
14.3 (previous 14.4)	No changes		
14.4 (previous 14.5)	If BP remains >130/80 mm Hg then the addition of a diuretic is recommended, followed by a calcium antagonist or other antihypertensive drugs. (Strength of Evidence = C)	If blood pressure remains >130/80 mm Hg then the addition of a thiazide diuretic is recommended, followed by a dihydropyridine calcium antagonist (eg, amlodipine or felodipine) or other antihypertensive drugs. (Strength of Evidence = C)	Modified to specify thiazide diuretic or dihydropyridine calcium channel antagonist
14.5 (previous 14.6)	No changes		
14.6 (previous 14.7)	If blood pressure remains >130/80 mm Hg, a noncardiac-depressing calcium antagonist (eg, amlodipine) may be considered or other antihypertensive medication doses increased. (Strength of Evidence = C)	If blood pressure remains >130/80 mm Hg, a dihydropyridine calcium antagonist (eg, amlodipine or felodipine) may be considered or other antihypertensive medication doses increased. (Strength of Evidence = C)	Modified to specify dihydropyridine
	Section 15: Management of Heart Failure in Special Populations		
15.1	No changes		
15.2	No changes		
15.3	No changes		
15.4	No changes		
15.5	No changes		
15.6		ARBs are recommended for administration to symptomatic and asymptomatic women with an LVEF ≤ 40% who are intolerant to ACE inhibitors for reasons other than hyperkalemia or renal insufficiency. (Strength of Evidence = A)	New recommendation
15.7		The combination of hydralazine/isosorbide dinitrate is recommended as standard therapy for African American women with moderate to severe HF symptoms who are on background neurohormonal inhibition. (Strength of Evidence = B)	New recommendation
15.8 (previous 15.6)	No changes		

15.9 (previous 15.7)	No changes	
15.10 (previous 15.8)	No changes	
15.11 (previous 15.9)	No changes	
	Section 16: Myocarditis: Current Treatment	
16.1	No changes	
16.2	No changes	
	Section 17: Genetic Evaluation of Cardiomyopathy	New section

Appendix B. Acronyms

Acronym	Meaning
ACE	angiotensin converting enzyme
ADA	American Diabetes Association
ADHF	acute decompensated heart failure
AF	atrial fibrillation
AHA/ACC	American Heart Association/American College of Cardiology
ALVD	asymptomatic left ventricular dysfunction
ARB	angiotensin receptor blocker
ARVD/C	arrhythmogenic right ventricular dysplasia/ cardiomyopathy
AV	arteriovenous
BMI	body mass index
BNP	B-type natriuretic peptide
BUN	blood urea nitrogen
CABG	coronary artery bypass graft
CAD	coronary artery disease
CHD	congenital heart disease
CI	confidence interval
CK-MM	creatinine kinase MM isoenzyme
COPD	chronic obstructive pulmonary disease
COX-2	cyclooxygenase-2
CPAP	continuous positive airway pressure
CPR	cardiopulmonary resuscitation
CR/XL	controlled release/extended release
CREST	a limited cutaneous form of scleroderma defined by calsinosis, Raynaud's syndrome, esophageal dysmotility, sclerodactyly, and telangiectasia
CRT	cardiac resynchronization therapy
CRT-D	cardiac resynchronization therapy device and defibrillator
CTR	cardiothoracic ratio
DASH	Dietary Approaches to Stop Hypertension
DBP	diastolic blood pressure
DCM	dilated cardiomyopathy
DNR	do not resuscitate
DVT	deep venous thrombosis
ECG	electrocardiogram
ED	emergency department
EP, EPS	electrophysiology, electrophysiology study
EVCPP	endoventricular circular patch plasty
FDC	familial dilated cardiomyopathy
GFR, eGFR	glomerular filtration rate, estimated glomerular filtration rate
HCM	hypertrophic cardiomyopathy
HF	heart failure
HFSA	Heart Failure Society of America
HR	hazard ratio
ICD	implantable cardioverter defibrillator
INR	international normalized ratio
JVP	jugular venous pressure
LA	left atrial
LMWH	low molecular weight heparin
LV	left ventricular
LVAD	left ventricular assist device
LVEF	left ventricular ejection fraction
LVH	left ventricular hypertrophy
LVNC	left ventricular noncompaction
MI	myocardial infarction
MRI	magnetic resonance imaging
NCEP	National Cholesterol Education Program
NIV	non-invasive ventilation
NSAID	non-steroidal anti-inflammatory drug
NT-proBNP	N-terminal pro-B-type natriuretic peptide
NYHA	New York Heart Association
OMIM	Online Mendelian Inheritance in Man (online resource)
OU	observation unit
PCI	percutaneous coronary intervention
PCWP	pulmonary capillary wedge pressure
PE	pulmonary embolism
PET-CT	positron emission tomography − computed tomography
PMI	point of maximal impulse
PND	paroxysmal nocturnal dyspnea
PPAR-α	peroxisome proliferator-activated receptor-alpha
PUFA	polyunsaturated fatty acids
PVC	premature ventricular contraction
QTc	QT interval corrected for heart rate
RAAS	renin-angiotensin-aldosterone system
RCM	restrictive cardiomyopathy
RV	right ventricular
SAECG	signal-averaged electrocardiogram
SAVER	surgical anterior ventricular endocardial restoration
SBP	systolic blood pressure
SCD	sudden cardiac death
SDC	serum digoxin concentration
SPECT	single-photon emission computed tomography
SSRI	selective serotonin reuptake inhibitors
STEMI	ST-elevation myocardial infarction
TNF-α	tumor necrosis factor-alpha
UFH	unfractionated heparin
USDA	United States Department of Agriculture
VE/VCO_2	ventilation equivalent of carbon dioxide (production slope)
VF	ventricular fibrillation
VT	ventricular tachycardia
Clinical Trials	
Acronym	**Full Trial Name**
ACCOMPLISH	Avoiding Cardiovascular Events Through Combination Therapy in Patients Living with Systolic Hypertension
ADHERE	Acute Decompensated Heart Failure National Registry (Registry)
AFFIRM	Atrial Fibrillation Follow-Up Investigation of Rhythm Management
A-HeFT	African-American Heart Failure Trial
ALLHAT	Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial
ALOFT	Aliskiren Observation of Heart Failure Treatment
B-CONVINCED	Beta Blocker Continuation Versus Interruption on Patients with Congestive Heart Failure Hospitalized for a Decompensation Episode
CANPAP	Canadian Continuous Positive Airway Pressure for Patients with Central Sleep Apnea and Heart Failure
CAPRICORN	Carvedilol Post-Infarct Survival Control in Left Ventricular Dysfunction
CARE-HF	Cardiac Resynchronization-Heart Failure
CHARM	Candesartan in Heart Failure Assessment of Reduction in Mortality and Morbidity (Also CHARM-Added, CHARM-Alternative, CHARM-Preserved)
CIBIS	Cardiac Insufficiency Bisoprolol Study
COACH	Coordinating Study Evaluating Outcomes of Advising and Counseling in Heart Failure
COMET	Carvedilol or Metoprolol European Trial
COMPANION	Comparison of Medical Therapy, Pacing, and Defibrillation in Chronic Heart Failure
CONSENSUS II	Cooperative New Scandinavian Enalapril Survival Study II
COPERNICUS	Carvedilol Prospective Randomized Cumulative Survival Study
DIG	Digitalis Investigation Group
EFFECT	Enhanced Feedback for Effective Cardiac Treatment (Evaluation Tool)
EPHESUS	Epleronone Post-Acute Myocardial Infarction Heart Failure Efficacy and Survival Study
ESCAPE	Evaluation Study of Congestive Heart Failure and Pulmonary Artery Catheterization Effectiveness
EUROPA	European Trial on Reduction of Cardiac Events with Perindopril in Stable Coronary Artery Disease
FAIR-HF	Ferinject Assessment in Patients with Iron Deficiency and Chronic Heart Failure
GISSI	Gruppo Italiano Per Lo Studio Della Sopravvivenza Nell'infarto Miocardico (GISSI-Prevenzione, GISSI-HF)
GUSTO-1	Global Utilization of Streptokinase and Tissue Plasminogen Activator for Occluded Coronary Arteries

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Appendix B. (*continued*)

HEART	Heart Failure Revascularization Trial
HELP	Hospitalized Elderly Longitudinal Project
HERS	Heart and Estrogen/Progestin Replacement Study
HF-ACTION	A Controlled Trial Investigating Outcomes of Exercise Training
HOBIPACE	Homburg Biventricular Pacing Evaluation
HOPE	Heart Outcomes Prevention Evaluation
HOT	Hypertension Optimal Treatment
INTERMACS	Interagency Registry for Mechanically Assisted Circulatory Support (Registry)
I-PRESERVE	Irbesartan in Heart Failure with Preserved Ejection Fraction
IRON-HF	Iron Supplementation in Heart Failure Patients with Anemia
ISIS-4	Fourth International Study of Infarct Survival
MADIT-CRT	Multi-Center Automatic Defibrillator Implantation Trial with Cardiac Resynchronization Therapy
MERIT-HF	Metoprolol CR?XL Randomized Intervention Trial in Congestive Heart Failure
MIRACLE	Multicenter Insync Clinical Study
MTT	Myocarditis Treatment Trial
MUSTT	Multicenter Unsustained Tachycardia Trial
NHANES	National Health and Nutrition Examination Survey Epidemiologic Follow-Up Study
OAT	Occluded Artery Trial
OPTIMAAL	Optimal Trial in Myocardial Infarction with the Angiotensin II Antagonist Losartan
OPTIME-HF	Outcomes of a Prospective Trial of Intravenous Milrinone for Exacerbations of Chronic Heart Failure
OPTIMIZE-HF	Organized Program to Initiate Lifesaving Treatment in Hospitalized Patients with Heart Failure (Registry)
PRIDE	N-Terminal Pro-BNP Investigation of Dyspnea in the Emergency Department
PRIMA	Can Pro-Brain-Natriuretic-Peptide Guided Therapy of Chronic Heart Failure Improve Heart Failure Morbidity and Mortality?
PROVED	Prospective Randomized Study of Ventricular Function and Efficacy of Digoxin
RADIANCE	Randomized Assessment of Digoxin on Inhibitors of the Angiotensin Converting System
RALES	Randomized Aldactone Evaluation Study
RED-HF	Reduction of Events with Darbepoetin Alfa in Heart Failure
REMATCH	Randomized Evaluation of Mechanical Assistance for the Treatment of Congestive Heart Failure
REVERSE	Resynchronization Reverses Remodeling in Systolic Left Ventricular Dysfunction
REVERT	Reversal of Ventricular Remodeling with Toprol-XL
SCD-HeFT	Sudden Cardiac Death in Heart Failure Trial
SENIORS	Study of the Effects of Nebivolol Intervention on Outcomes and Rehospitalization in Seniors with Heart Failure
SOLVD	Studies of Left Ventricular Dysfunction
STARS-BNP	Systolic Heart Failure Treatment Supported By BNP
STICH	Surgical Treatment for Ischemic Heart Failure
SUPPORT	Study to Understand Prognoses and Preferences for Outcomes and Risks of Treatment
TIME-CHF	Trial of Intensified Vs Standard Medical Therapy in Elderly Patients with Congestive Heart Failure
UKPDS	United Kingdom Prospective Diabetes Study
Val-HeFT	Valsartan Heart Failure Trial
VALIANT	The Valsartan in Acute Myocardial Infarction Trial
V-HeFT	Vasodilator Heart Failure Trial
VMAC	Vasodilator in the Management of Acute Heart Failure
WASH	Warfarin/Aspirin Study in Heart Failure
WATCH	Warfarin and Antiplatelet Therapy in Chronic Heart Failure

Appendix C. Financial Disclosure

Name	Consulting Fees/Honoraria	Speaker's Bureau	Research Grants	Equity Interests/ Stock/Stock Options	Equity Interests	Royalty Income	Non-Royalty Payments	Other Financial Benefit	Salary	Intellectual Property Rights	Fellowship Support
Nancy M. Albert, R.N., Ph.D	Medtronic										
Inder S. Anand, M.D., Ph.D.	Amgen Pharmaceuticals, Boston Scientific, Corventis, CVRx, Merck, Medtronic, N30, Paracor	Novartis Pharma-ceuticals	CVRx, Novartis Pharmaceuticals, Paracor						VA Medical Center		
J. Malcolm O. Arnold, M.D.	Abbott, Boehringer Ingelheim, GlaxoSmithKline, Merck-Frosst, Novartis, Pfizer										
John P. Boehmer, M.D.	Boston, Scientific, Medtronic, St. Jude		Boston Scientific, CardioMEMS, Medtronic, Novartis, Paracor								
John C. Burnett, M.D.	Anexon, Nile Therapeutics, Otsuka		Anexon, Bayer, BioRad, Merck, Nile Therapeutics, Trevena			Anexon, Nile Therapeutics					
John Chin, M.D.	Gilead, Otsuka	Boston Scientific, Eli Lilly, Gilead, Novartis									
Jay N. Cohn, M.D.			GlaxoSmithKline	CPC, LLC	HDT, Inc.	MLHFQ, NitroMed					
Sean P. Collins, M.D., MSc	Abbott Point-of-Care, Astellas, Bayer, Corthera, The Medicines Company, Otsuka		Abbott Point-of-Care, BRAHMS Diagnostics, National Institutes of Health/NHLBI								
Justin A. Ezekowitz, MBBCh	Amgen, Bristol-Myers Squibb, Pfizer		Amgen, Bristol-Myers Squibb, Merck, Ortho-Biotech/Johnson & Johnson								
Thomas Force, M.D.		Merck Schering Plough/Merck						GlaxoSmithKline			
Bart Galle, Ph.D.	disclosures: none										

Michael M. Givertz, M.D.	Cardioxyl		Asahi Kasei								
Sarah J. Goodlin, M.D.	Servier		Boston Scientific CARE, St. Jude Medical Foundation								
Barry H. Greenberg, M.D.	Biogen Idec, CardioMEMS, Corthera, Cytokinetics, GlaxoSmithKline, Otsuka, Paracor, St. Jude, Zensun	Gilead, Merck, Novartis, sanofi-aventis									
Ray E. Hershberger, M.D.	disclosures: none										
Steven R. Houser, Ph.D.	disclosures: none										
Jonathan G. Howlett, M.D.	AstraZeneca, Merck, Novartis, Schering, Servier	AstraZeneca, Merck, Novartis, Schering, Servier	AstraZeneca, Medtronic, Merck, Novartis, Schering, Servier								
Sharon A. Hunt, M.D.	disclosures: none										
Mariell Jessup, M.D.	Medtronic	Boston Scientific									
Stuart D. Katz, M.D.	Amgen, Dura Heart Terumo, Merck, Paracor										
Marc Klapholz, M.D.	GlaxoSmithKline, Medtronic, Paracor, St. Jude, Schering	GlaxoSmithKline									
Marvin W. Kronenberg, M.D.				Cardiovascular Services of America							
JoAnn Lindenfeld, M.D.	Astellas, Boston Scientific, Forest, Medtronic, N30		Merck								
Douglas L. Mann, M.D.	ARMGO Pharmaceuticals, Medtronic, Miragen, Nile Therapeutics, PeriCor Therapeutics				Miragen						

(*continued on next page*)

Appendix C. (*continued*)

Name	Consulting Fees/Honoraria	Speaker's Bureau	Research Grants	Equity Interests/ Stock/Stock Options	Equity Interests	Royalty Income	Non-Royalty Payments	Other Financial Benefit	Salary	Intellectual Property Rights	Fellowship Support
Barry M. Massie, M.D.	ARCA, Boehringer, Bristol-Myers Squibb, Corthera, Cytokinetics, Duke Clinical Research Institute, Merck, Nile Therapeutics, Novartis, sanofi-aventis, St. Jude, Takeda, Trevena	Merck									
Mandeep R. Mehra, M.D.	Geron, Johnson & Johnson, Medtronic, Pericor, Solvay, St. Jude		National Institutes of Health								
Luisa Mestroni, M.D.		M01 RR00051-1575						University of Colorado (employee)			
Alan B. Miller, M.D.	disclosures: none										
Debra K. Moser, R.N., DNSc.	disclosures: none										
Mariann R. Piano, R.N., Ph.D.	disclosures: none										
Richard J. Rodeheffer, M.D.	disclosures: none										
Joseph G. Rogers, M.D.	Forrest Pharmaceuticals, Thoratec	Boston Scientific, Medtronic									
Christine E. Seidman, M.D.			HHMI & NIH								
Randall C. Starling, M.D., MPH	BioControl, Medtronic, Novartis		Biotronik, Medtronic, Novartis, Thoratec	CardioMEMS							Medtronic
William G. Stevenson, M.D.	disclosures: none										

Wendy Gattis Stough, Pharm.D.	ARCA Discovery, Inc., Gilead Sciences, Inc., GlaxoSmithKlline, Heart Failure Society of America, Medtronic, Otsuka, Scios										
W.H. Wilson Tang, M.D.	Medtronic, Merck & Company		Abbott Laboratories								
Matthew R.G. Taylor, M.D., Ph.D.		Genzyme Therapeutics	Muscular Dystrophy Association/March of Dimes/Genzyme Therapeutics								
John R. Teerlink, M.D.	Abbott Laboratories, BAS Medical/ Corthera, Biogen Idec, Bristol-Myers Squibb, CardioDynamics, CardioMEMS, CoGeneSys, Cytokinetics, Geron, GlaxoSmithKline, Icon Medical Imaging, Indigo Pharma, Kowa Pharma, Luitpold Pharma, Merck, Momentum Research, Nile Therapeutics, Novartis, sanofi-aventis, Scios/ Johnson & Johnson		Abbott Laboratories, BAS Medical/Corthera, Bristol-Myers Squibb, Cytokinetics, GlaxoSmithKline, Merck, National Institutes of Health, Novartis, sanofi-aventis	Cytokinetics							
Jeffery A. Towbin, M.D.	disclosure: none										
Mary N. Walsh, M.D.	ARCA, Boston Scientific, EMERGE, Medtronic, United Health Care										
Clyde W. Yancy, M.D.	disclosures: none										
Cheryl Yano	disclosures: none										
Michael R. Zile, M.D.	ABIM, BMS, CorAssist, CVRx, DC Devices, Gilead, Medtronic, Merck, N30, Novartis, OCD/J&J, sanofi-aventis, Up-To-Date		BMS, Boston, Scientific, CVRx, Department of VA, Gilead, Medtronic, Merck, National Heart, Lung and Blood Institute, Novartis, OCD/J&J, Pfizer, sanofi-aventis						Department of VA, MUSC, National Heart, Lung and Blood Institute	MUSC, OCD/ J&J	

HFSA 2010 Comprehensive Heart Failure Practice Guideline

HEART FAILURE SOCIETY OF AMERICA

St. Paul, Minnesota

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ABSTRACT

Heart failure (HF) is a syndrome characterized by high mortality, frequent hospitalization, reduced quality of life, and a complex therapeutic regimen. Knowledge about HF is accumulating so rapidly that individual clinicians may be unable to readily and adequately synthesize new information into effective strategies of care for patients with this syndrome. Trial data, though valuable, often do not give direction for individual patient management. These characteristics make HF an ideal candidate for practice guidelines. The 2010 Heart Failure Society of America comprehensive practice guideline addresses the full range of evaluation, care, and management of patients with HF.

Key Words: Heart failure, practice guidelines.

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A copy of the HFSA Comprehensive Heart Failure Practice Guideline can be found at www.onlinejcf.com

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Section 1: Development and Implementation of a Comprehensive Heart Failure Practice Guideline

Introduction

Heart failure (HF) is a syndrome characterized by high mortality, frequent hospitalization, poor quality of life, and multiple comorbidities. As a result, heart failure management inevitably involves both a multidimensional assessment process and a complex therapeutic regimen. Knowledge about the pathophysiology and treatment of HF continues to accumulate very rapidly so that individual clinicians may be unable to readily and adequately synthesize new information into effective principles of care for patients with this syndrome. Trial data, though valuable, often do not give adequate direction for individual patient management.

Given the complex and changing picture of HF and the accumulation of evidence-based HF therapy, it is not possible for the clinician to rely solely on personal experience and observation to guide therapeutic decisions. This situation is exacerbated because HF is now a chronic condition in most patients, meaning that the outcome of therapeutic decisions might not be apparent for several years. The natural history and prognosis of individual patients differs considerably, making it difficult to generalize. Treatments might not dramatically improve symptoms of the disease process, yet might prevent of delay its progression and the occurrence of morbid events and deaths. The assessment of specific therapeutic outcomes is complicated by the potential differential impact of various cotherapies.

The complexity of HF, its high prevalence, and the availability of many therapeutic options make it an ideal area for practice guidelines. Additional assumptions driving the development of HF guidelines are presented in Table 1.1.

The first HF guideline developed by the Heart Failure Society of America (HFSA) had a narrow scope, concentrating on the pharmacologic treatment of chronic, symptomatic left ventricular dysfunction.[1] It did not consider subsets of the clinical syndrome of HF, such as acute decompensated HF and ''diastolic dysfunction,'' or issues such as prevention. The subsequent comprehensive clinical practice guideline published in 2006 addressed a full range of topics including prevention, evaluation, disease management, and pharmacologic and device therapy for patients with HF.[2] The 2010 guideline updates and expands each of these areas and adds a section on the Genetic Evaluation of Cardiomyopathy published separately in 2009.[3] The discussion of end of life management has also been considerably expanded.

HFSA Guideline Approach to Medical Evidence

Two considerations are critical in the development of practice guidelines: assessing strength of evidence and determining strength of recommendation. Strength of evidence is determined both by the type of evidence available and the assessment of validity, applicability, and certainty of a specific type of evidence. Following the lead of previous guidelines, strength of evidence in this guideline is heavily dependent on the source or type of evidence used. The HFSA guideline process has used three grades (A, B, or C) to characterize the type of evidence available to support specific recommendations (Table 1.2).

It must be recognized, however, that the evidence supporting recommendations is based largely on population responses that may not always apply to individuals within the population. Therefore, the totality of data may support overall benefit of one treatment over another but cannot assure that all patients will respond similarly. Thus, guidelines can best serve as evidence-based recommendations for management, not as mandates for management in every patient. Furthermore, it must be recognized that trial data on which recommendations are based have often been carried out with background therapy not comparable to therapy in current use. Therefore, physician decisions regarding the management of individual patients may not always precisely match the recommendations. A knowledgeable physician who integrates the guidelines with pharmacologic and physiologic insight and knowledge of the individual being treated should provide the best patient management.

Strength of Evidence A. Randomized controlled clinical trials provide what is considered the most valid form of guideline evidence. Some guidelines require at least 2 positive randomized clinical trials before the evidence for a recommendation can be designated level A. The HFSA guideline committee has occasionally accepted a single randomized, controlled, outcome-based clinical trial as sufficient for level A evidence when the single trial is large with a substantial number of endpoints and has consistent and robust outcomes. However, randomized clinical trial data, whether derived from one or multiple trials, have not been taken simply at face value. They have been evaluated for: (1) endpoints studied, (2) level of significance, (3) reproducibility of findings, (4) generalizability of study

Table 1.1. Assumptions Underlying HFSA Practice Guideline

Clinical decisions must be made.
Correct course of action may not be readily apparent.
Multiple non-pharmacologic, pharmacologic, and device therapies are available.
Reasonably valid methods exist to address knowledge base and evaluate medical evidence.
Data beyond randomized clinical trials exist that enhance medical decision making.
Uncertainties remain concerning approaches to treatment after review of totality of medical evidence.
Expert opinion has a role in management decisions when Strength of Evidence A data are not available to guide management.
A consensus of experts remains the best method of management recommendations when Strength of Evidence A data are not available.

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Table 1.2. Relative Weight of Evidence Used to Develop HFSA Practice Guideline

Hierarchy of Types of Evidence	
Level A	Randomized, Controlled, Clinical Trials
	May be assigned based on results of a single methodologically rigorous trial
Level B	Cohort and Case-Control Studies
	Post hoc, subgroup analysis, and meta-analysis
	Prospective observational studies or registries
Level C	Expert Opinion
	Observational studies-epidemiologic findings
	Safety reporting from large-scale use in practice

results, and (5) sample size and number of events on which outcome results are based.

Strength of Evidence B. The HFSA guideline process also considers evidence arising from cohort studies or smaller clinical trials with physiologic or surrogate endpoints. This level B evidence is derived from studies that are diverse in design and may be prospective or retrospective in nature. They may involve subgroup analyses of clinical trials or have a case control or propensity adjusted design using a matched subset of trial populations. Dose-response studies, when available, may involve all or a portion of the clinical trial population. Evidence generated from these studies has well-recognized, inherent limitations. Nevertheless, their value is enhanced through attention to factors such as pre-specification of hypotheses, biologic rationale, and consistency of findings between studies and across different populations.

Strength of Evidence C. The present HFSA guideline makes extensive use of expert opinion, or C-level evidence. The need to formulate recommendations based on expert opinion is driven primarily by a paucity of evidence in areas critical to a comprehensive guideline or by evidence derived from a study population not fully representative of the broad spectrum of HF patients. For example, the diagnostic process and the steps used to evaluate and monitor patients with established HF have not been the subject of clinical studies that formally test the accuracy of one approach versus another. In addition, trials often enroll patients that differ from the general HF population in age or gender distribution and in background therapies. In situations such as these, recommendations must be based on expert opinion or go unaddressed.

The value of expert opinion as a form of evidence remains disputed. Many contend that expert opinion is a weak form of observational evidence, based on practice experience and subject to biases and limitations. Advocates believe expert opinion represents a complex synthesis of observational insights into disease pathophysiology and the benefits of therapy in broad populations of patients. They stress the value of the interchange of experience and ideas among colleagues, who collectively treat thousands of patients. Through contact with numerous individual health care providers who may discuss patients with them, experts are exposed to rare safety issues and gain insight into the perceptions of practitioners concerning the efficacy of particular treatments across a wide spectrum of HF.

Despite the case that can be made for its value, recommendations based on expert opinion alone have been limited to those circumstances when a definite consensus could be reached across the guideline panel and reviewers.

HFSA Guideline Approach to Strength of Recommendation

Determining Strength. Although level of evidence is important, the strength given to specific recommendations is critical. The process used to determine the strength of individual recommendations is complex. The goal of guideline development is to achieve the best recommendations for evaluation and management, considering not only efficacy, but the cost, convenience, side effect profile, and safety of various therapeutic approaches. The HFSA guideline committee often determined the strength of a recommendation by the ''totality of evidence,'' which is a synthesis of all types of available data, pro and con, about a particular therapeutic option.

Totality of Evidence. Totality of evidence includes not only results of clinical trials, but also expert opinion and findings from epidemiologic and basic science studies. Agreement among various types of evidence, especially from different methodologies, increases the likelihood that a particular therapy is valuable. Although many equate evidence-based medicine with the results of a few individual clinical trials, the best judgment seems to be derived from a careful analysis of all available trial data combined with integration of results from the basic laboratory and the findings of epidemiologic studies.

Scale of Strength. The HFSA guideline employs the categorization for strength of recommendation outlined in Table 1.3. There are several degrees of favorable recommendations and a single category for therapies felt to be not effective. The phrase ''is recommended'' should be taken to mean that the recommended therapy or management process should be followed as often as possible in individual patients. Exceptions are carefully delineated. ''Should be considered'' means that a majority of patients should receive the intervention, with some discretion

Table 1.3. HFSA System for Classifying the Strength of Recommendations

''Is recommended''	Part of routine care
	Exceptions to therapy should be minimized
''Should be considered''	Majority of patients should receive the intervention
	Some discretion in application to individual patients should be allowed
''May be considered''	Individualization of therapy is indicated
''Is not recommended''	Therapeutic intervention should not be used

involving individual patients. ''May be considered'' means that individualization of therapy is indicated (Table 1.3). When the available evidence is considered to be insufficient or too premature, or consensus fails, issues are labeled unresolved and included as appropriate at the end of the relevant section.

Process of Guideline Development

Key steps in the development of this guideline are listed in Table 1.4. Having determined the broad scope of the current guideline, subcommittees of the guideline committee were formed for each section of the guideline. Literature searches with relevant key words and phrases for each guideline section were provided to members of the subcommittees and the full Guideline Committee. Members of each subcommittee were asked to review the search and identify any additional relevant medical evidence for each assigned section. Changes in recommendation and background were carried out by each subcommittee with conference calls directed by the Guideline Committee chair. Each section was presented for comments and consensus approval to the Guideline Committee. Once subsections were complete, the Executive Council reviewed and commented on each section and these comments were returned to the Guideline Committee for changes and once complete, for final approval by the Executive Council. Appendix A provides a grid showing changes to the 2006 guideline.

Consensus. The development of a guideline involves the selection of individuals with expertise and experience to drive the process of formulating specific recommendations and producing a written document. The role of these experts goes well beyond the formulation of recommendations supported by expert opinion.

Experts involved in the guideline process must function as a collective, not as isolated individuals. Expert opinion is not always unanimous. Interpretations of data vary. Disagreements arise over the generalizability and applicability of trial results to various patient subgroups. Experts are influenced by their own experiences with particular therapies, but still generally agree on the clinical value of trial data. Discomfort with the results of trials reported as positive or negative generally focus on factors that potentially compromise the evidence. Unfortunately, there are no absolute rules for downgrading or upgrading trial results or for deciding whether the limitations of the trial are sufficient to negate what has been regarded as a traditionally positive or negative statistical result.

Table 1.4. Steps in the Development of the 2010 HFSA Practice Guideline

Determine the scope of the practice guideline
Form subcommittees with expertise for each guideline section
Perform literature search relevant to each guideline section and distribute to subcommittee and committee members
Solicit additional relevant information from subcommittee and committee members for each subsection
Formulate new recommendations and revise previous recommendations assigning Strength of Recommendation and Strength of Evidence
Form consensus of subcommittee for each section by conference call
Assign writing of additional or revised background by subcommittee
Full committee review of each section with revisions by subcommittee
Review of each completed section by Executive Council with revisions made by full committee and returned to Executive Council for final approval.
Disseminate document
Update document as changes are necessary

The HFSA guideline committee sought resolution of difficult cases through consensus building. An open, dynamic discussion meant that no single voice was allowed to dominate. Written documents were essential to this process, because they provided the opportunity for feedback from all members of the group. On occasion, consensus of opinion was sufficient to override positive or negative results of almost any form of evidence. The HFSA process had a strong commitment to recommendations based on objective evidence rigorously reviewed by a panel of experts.

Issues that caused particular difficulty for the HFSA guideline process usually were some of the more important ones faced by the committee, because they mirrored those that are often most challenging to clinicians in day-to-day practice. The foundation of the HFSA guideline process was the belief that the careful judgment of recognized opinion leaders in these controversial areas is more likely to be correct than ad hoc decisions made ''on the spot'' by physicians in practice.

The involvement of many groups in the development of this guideline helped avoid the introduction of real or perceived bias, which can be personal, practice-based, or based on financial interest. Committee members and reviewers from the Executive Council received no direct financial support from the HFSA or any other source for the development of the guideline. Support was provided by the HFSA administrative staff, but the writing of the document was performed on a volunteer basis primarily by the Committee. Information concerning financial relationships that might represent conflicts of interest was collected annually from all members of the Guideline Committee and the Executive Council. Current relationships are shown in Appendix C.

Dissemination and Continuity. The value of a practice guideline is significantly influenced by the scope of its dissemination. The first and second HFSA guidelines were available on the Internet, and thousands of copies were downloaded. The current document will be accessible on the Internet both for file transfer and as a hypertext source of detailed knowledge concerning HF.

An important final consideration is the continuity of the guideline development process. The intent is to create a ''living document'' that will be updated and amended as necessary to ensure continuing relevance. The rapid development of new knowledge in HF from basic and clinical research and the continuing evolution of pharmacologic and device therapy for this condition provides a strong mandate

for timely updates. The HFSA intends to undertake targeted reviews and updates in areas where new research has implications for practice. Section 17: The Genetic Evaluation of Cardiomyopathy is an example of this policy.

Summary

Practice guidelines have become a major part of the clinical landscape and seem likely to become more rather than less pervasive. Some may perceive guidelines as another mechanism for process management or as another instrument for cost control. But there is a more patient-centered rationale for their development, especially for a common, potentially debilitating, and often fatal syndrome such as HF. Despite advances in clinical trial methodology and the extensive use of studies to evaluate therapeutics and the care process, essential elements of the management process remain undefined for many clinical problems. HF is no exception. Traditionally, management guidelines were determined on an ad hoc basis by physicians and other health care providers in the field. The development and utilization of practice guidelines has emerged as an alternative strategy. The methodology of guideline development needs improvement, but when these documents are properly conceived and formulated, their importance to patient care seems evident. This HFSA guideline on HF is designed as a ''living document,'' which will continue to serve as a resource for helping patients with HF.

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Appendix A. Comparison of the 2006 and 2010 HFSA Guideline

	2006 Guideline Recommendation	2010 Guideline Recommendation	Comments
	Section 3: Prevention of Ventricular Remodeling, Cardiac Dysfunction, and Heart Failure		
3.1	A careful and thorough clinical assessment, with appropriate investigation for known or potential risk factors, is recommended in an effort to prevent development of LV remodeling, cardiac dysfunction, and HF. These risk factors include, but are not limited to, hypertension, hyperlipidemia, atherosclerosis, diabetes mellitus, valvular disease, obesity, physical inactivity, excessive alcohol intake, and smoking. (Strength of Evidence = A)	A careful and thorough clinical assessment, with appropriate investigation for known or potential risk factors, is recommended in an effort to prevent development of LV remodeling, cardiac dysfunction, and HF. These risk factors include, but are not limited to, hypertension, hyperlipidemia, atherosclerosis, diabetes mellitus, valvular disease, obesity, physical inactivity, excessive alcohol intake, dietary choices, and smoking. (Strength of Evidence = A)	Addition of dietary choices to list of risk factors
3.2	No changes		
3.3	No changes		
3.4	No changes		
	Section 4: Evaluation of Patients for Ventricular Dysfunction and Heart Failure		
4.1	Evaluation with a routine history, physical examination, chest x-ray, and electrocardiogram (ECG) is recommended in patients with the medical conditions or test findings listed in Table 4.1. (Strength of Evidence = B)	Evaluation for clinical manifestations of HF with a routine history and physical examination is recommended in patients with the medical conditions or test findings listed in Table 4.1. (Strength of Evidence = B)	Modification of wording and deletion of chest x-ray and ECG (retained in Table 4.1)
4.2	Assessment of Cardiac Structure and Function. Echocardiography with Doppler is recommended to determine LV size and function in patients without signs or symptoms suggestive of HF who have the risk factors listed in Table 4.2. (Strength of Evidence = B)	Assessment of Cardiac Structure and Function. Echocardiography with Doppler is recommended to determine cardiac structure and function in asymptomatic patients with the disorders or findings listed in Table 4.2. (Strength of Evidence = B)	Modification of wording and terminology
4.3	Determination of plasma B-type natriuretic peptide (BNP) or N-terminal pro-BNP concentration is not recommended as a routine part of the evaluation for structural heart disease in patients at risk but without signs or symptoms of HF. (Strength of Evidence = B)	Routine determination of plasma BNP or NT-proBNP concentration as part of a screening evaluation for structural heart disease in asymptomatic patients is not recommended. (Strength of Evidence = B)	Modification of wording and terminology
4.4	Symptoms Consistent with HF. The symptoms listed in Table 4.3 suggest the diagnosis of HF. It is recommended that each of these symptoms be solicited and graded in all patients in whom the diagnosis of HF is being considered. (Strength of Evidence = B)	Symptoms Consistent with HF. The symptoms listed in Table 4.3 suggest the diagnosis of HF. It is recommended that each of these symptoms be elicited in all patients in whom the diagnosis of HF is being considered. (Strength of Evidence = B)	Modification of wording and addition of depression to Table 4.3
4.5	Physical Examination. It is recommended that patients suspected of having HF undergo careful physical examination with determination of vital signs and be carefully evaluated for signs and symptoms shown in Table 4.4. (Strength of Evidence = C)	Physical Examination. It is recommended that patients suspected of having HF undergo careful physical examination with determination of vital signs and careful evaluation for signs shown in Table 4.4. (Strength of Evidence = B)	Modification of wording and change in Strength of Evidence from C to B and addition of reduced cardiac output and arrhythmia to cardiac abnormalities in Table 4.4
4.6	It is recommended that BNP or NT-proBNP levels be assessed in all patients suspected of having HF when the diagnosis is not certain. (Strength of Evidence = B)	It is recommended that BNP or NT-proBNP levels be assessed in all patients suspected of having HF, especially when the diagnosis is not certain. (Strength of Evidence = A)	Modification of wording and change in Strength of Evidence from B to A

(*continued on next page*)

Appendix A. (*continued*)

	2006 Guideline Recommendation	2010 Guideline Recommendation	Comments
4.7	The differential diagnoses in Table 4.5 should be considered as alternative explanations for signs and symptoms consistent with HF. (Strength of Evidence = C)	Differential Diagnosis. The differential diagnoses in Table 4.5 should be considered as alternative explanations for signs and symptoms consistent with HF. (Strength of Evidence = B)	Modification of wording and change in Strength of Evidence from C to B and addition of chronic kidney disease and thyroid abnormalities to Table 4.5
4.8	No changes		
4.9	Symptoms. In addition to symptoms characteristic of HF, the following symptoms should be considered in the diagnosis of HF: • Angina • Symptoms of possible cerebral hypoperfusion, including syncope, pre-syncope, or lightheadedness • Symptoms suggestive of embolic events • Symptoms suggestive of sleep-disordered breathing (Strength of Evidence = C)	Symptoms. In addition to symptoms characteristic of HF (dyspnea, fatigue, decreased exercise tolerance, fluid retention), evaluation of the following symptoms should be considered in the diagnosis of HF: • Angina • Symptoms suggestive of embolic events • Symptoms suggestive of sleep-disordered breathing • Symptoms suggestive of arrhythmias, including palpitations • Symptoms of possible cerebral hypoperfusion, including syncope, presyncope, or lightheadedness (Strength of Evidence = B)	Clarification of HF symptoms and addition of arrhythmia to list of symptoms and change in Strength of Evidence from C to B
4.10	No changes		
4.11	The degree of volume excess is a key consideration during treatment. It is recommended that it be routinely assessed by determining: • Presence of paroxysmal nocturnal dyspnea or orthopnea • Daily weights and vital signs with assessment for orthostatic changes • Presence and degree of rales, S3 gallop, jugular venous pressure elevation, positive hepatojugular reflux, edema, and ascites (Strength of Evidence = B)	Volume Status. The degree of volume excess is a key consideration during treatment. It is recommended that it be routinely assessed by determining: • Presence of paroxysmal nocturnal dyspnea or orthopnea • Presence of dyspnea on exertion • Daily weights and vital signs with assessment for orthostatic changes • Presence and degree of rales, S3 gallop, jugular venous pressure elevation, hepatic enlargement and tenderness, positive hepatojugular reflux, edema, and ascites (Strength of Evidence = B)	Addition of presence of dyspnea on exertion and hepatic enlargement/tenderness to list of assessments
4.12	It is recommended that the following laboratory tests be obtained routinely in patients being evaluated for HF: serum electrolytes, blood urea nitrogen, creatinine, glucose, calcium, magnesium, lipid profile (low-density lipoprotein cholesterol, high-density lipoprotein cholesterol, triglycerides), complete blood count, serum albumin, liver function tests, urinalysis, and thyroid function. (Strength of Evidence = B)	Standard Laboratory Tests. It is recommended that the following laboratory tests be obtained routinely in patients being evaluated for HF: serum electrolytes, blood urea nitrogen, creatinine, glucose, calcium, magnesium, fasting lipid profile (low-density lipoprotein cholesterol, high-density lipoprotein cholesterol, triglycerides), complete blood count, serum albumin, uric acid, liver function tests, urinalysis, and thyroid function. (Strength of Evidence = B)	Addition of uric acid to list of standard laboratory tests
4.13	It is recommended that all patients with HF have an ECG performed to: • Assess cardiac rhythm and conduction • Detect LV hypertrophy • Evaluate QRS duration, especially when ejection fraction (EF) <35% • Detect evidence of myocardial infarction or ischemia (Strength of Evidence = B)	Electrocardiogram (ECG). It is recommended that all patients with HF have an ECG performed to: • Assess cardiac rhythm and conduction (in some cases, using Holter monitoring or event monitors) • Assess electrical dyssynchrony (wide QRS or bundle branch block), especially when left ventricular ejection fraction (LVEF) <35% • Detect LV hypertrophy or other chamber enlargement • Detect evidence of MI or ischemia • Assess QTc interval, especially with drugs that prolong QT intervals (Strength of Evidence = B)	Addition of electrical dyssynchrony and QTc interval to list of ECG assessments

4.14	It is recommended that all patients with HF have a posteroanterior and lateral chest X-ray examination for determination of heart size, evidence of fluid overload, and detection of pulmonary and other diseases. (Strength of Evidence = B)	Chest X-Ray. It is recommended that all patients with HF have a posteroanterior and lateral chest X-ray examination for determination of heart size, evidence of fluid overload, detection of pulmonary and other diseases, and appropriate placement of implanted cardiac devices. (Strength of Evidence = B)	Addition of placement of implanted cardiac devices to list of chest x-rays assessments
4.15	Additional Laboratory Tests. It is recommended that patients with no apparent etiology of HF or no specific clinical features suggesting unusual etiologies undergo additional directed blood and laboratory studies to determine the cause of HF. (Strength of Evidence = C)	Additional Laboratory Tests. It is recommended that patients with no apparent etiology of HF or no specific clinical features suggesting unusual etiologies undergo additional directed blood and laboratory studies to determine the cause of HF. (Strength of Evidence = B)	Change in Strength of Evidence from C to B
4.16		Evaluation of myocardial ischemia is recommended in those who develop new-onset LV systolic dysfunction especially in the setting of suspected myocardial ischemia or worsening symptoms with pre-existing CAD. The choice of testing modality should depend on the clinical suspicion and underlying cardiac risk factors. Coronary angiography should be considered when pre-test probability of underlying ischemic cardiomyopathy is high and an invasive coronary intervention may be considered. (See Section 13 for specific clinical situations and Strength of Evidence)	New recommendation
4.17 (previous 4.16)	Exercise testing is not recommended as part of routine evaluation in patients with HF. Specific circumstances in which maximal exercise testing with measurement of expired gases should be considered include: • Assessing disparity between symptomatic limitation and objective indicators of disease severity • Distinguishing non–HF-related causes of functional limitation, specifically cardiac versus pulmonary • Considering candidacy for cardiac transplantation or mechanical intervention • Determining the prescription for cardiac rehabilitation • Addressing specific employment capabilities Exercise testing for inducible abnormality in myocardial perfusion or wall motion abnormality should be considered to screen for the presence of coronary artery disease with inducible ischemia. (Strength of Evidence = C)	Exercise testing for functional capacity is not recommended as part of routine evaluation in patients with HF. Specific circumstances in which maximal exercise testing with measurement of expired gases should be considered include: • Assessing disparity between symptomatic limitation and objective indicators of disease severity • Distinguishing non HF-related causes of functional limitation, specifically cardiac versus pulmonary • Considering candidacy for cardiac transplantation or mechanical circulatory support • Determining the prescription for cardiac rehabilitation • Addressing specific employment capabilities (Strength of Evidence = C)	Modification of wording and deletion of recommendation for exercise testing for inducible abnormality in myocardial perfusion or wall motion abnormality
4.18 (previous 4.17)	No changes		
4.19 (previous 4.18)	It is recommended that clinical evaluation at each followup visit include the assessments listed in Table 4.9. (Strength of Evidence = B) These assessments should include the same symptoms and signs assessed during the initial evaluation. (Strength of Evidence = C)	It is recommended that clinical evaluation at each follow-up visit include determination of the elements listed in Table 4.9. (Strength of Evidence = B). These assessments should include the same symptoms and signs assessed during the initial evaluation. (Strength of Evidence = B)	Change (in second part of recommendation) Strength of Evidence from C to B

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Appendix A. (*continued*)

	2006 Guideline Recommendation	2010 Guideline Recommendation	Comments
4.20 (previous 4.19)	Routine reevaluation of cardiac function by noninvasive or invasive methods is not recommended. Repeat measurements of ventricular volume and EF should be considered under limited circumstances: • After at least 3 months of medical therapy when prophylactic ICD placement is being considered to confirm that EF criteria are still met. (Strength of Evidence = B) • In patients who show substantial clinical improvement (for example, in response to b-blocker treatment). Such change may denote improved prognosis, although it does not in itself mandate alteration or discontinuation of specific treatments. (Strength of Evidence = C) Repeat determination of EF is usually unnecessary in patients with previously documented LV dilation and low EF who manifest worsening signs or symptoms of HF. Repeat measurement should be considered when it is likely to prompt a change in patient management, such as cardiac transplantation. (Strength of Evidence = C)	In the absence of deteriorating clinical presentation, repeat measurements of ventricular volume and LVEF should be considered in these limited circumstances: • When a prophylactic implantable cardioverter defibrillator (ICD) or CRT device and defibrillator (CRT-D) placement is being considered in order to determine that LVEF criteria for device placement are still met after medical therapy (Strength of Evidence = B) • When patients show substantial clinical improvement (for example, in response to beta blocker treatment or following pregnancy in patients with peripartum cardiomyopathy). Such change may denote improved prognosis, although it does not in itself mandate alteration or discontinuation of specific treatments (see Section 7). (Strength of Evidence = C) • In alcohol and cardiotoxic substance abusers who have discontinued the abused substance. (Strength of Evidence = C) • In patients receiving cardiotoxic chemotherapy. (Strength of Evidence = B) Repeat determination of LVEF is usually unnecessary in patients with previously documented LV dilatation and low LVEF who manifest worsening signs or symptoms of HF, unless the information is needed to justify a change in patient management (such as surgery or device implantation). (Strength of Evidence = C)	Modifications of recommendation throughout
4.21 (previous 4.20)	It is recommended that reevaluation of electrolytes and renal function occur at least every 6 months in clinically stable patients and more frequently after changes in therapy or with evidence of change in volume status. More frequent assessment of electrolytes and renal function is recommended in patients with severe HF, those receiving high doses of diuretics, and those who are clinically unstable. (Strength of Evidence = C) (See Section 7 for recommendations regarding patients on angiotensin receptor blockers.)	It is recommended that reevaluation of electrolytes and renal function occur at least every 6 months in clinically stable patients and more frequently following changes in therapy or with evidence of change in volume status. More frequent assessment of electrolytes and renal function is recommended in patients with severe HF, those receiving high doses of diuretics, those on aldosterone antagonists, and those who are clinically unstable. (Strength of Evidence = C) (See Section 7 for recommendations regarding patients on angiotensin receptor blockers.)	Addition of aldosterone antagonists to list of patients in whom more frequent assessment of electrolytes and renal function is recommended.
	Section 5: Management of Asymptomatic Patients with Reduced LVEF		
5.1	It is recommended that all patients with ALVD exercise regularly according to a physician-directed prescription to avoid general deconditioning; to improve weight, blood pressure, and diabetes control; and to reduce cardiovascular risk. (Strength of Evidence = C)	It is recommended that all patients with ALVD exercise regularly according to a physician-directed prescription to avoid general deconditioning; to optimize weight, blood pressure, and diabetes control; and to reduce cardiovascular risk. (Strength of Evidence = C)	Minor wording modification
5.2	No changes		
5.3	It is recommended that alcohol consumption be discouraged in patients with ALVD. Abstinence is recommended if there is a current habit or history of excessive alcohol intake. (Strength of Evidence = C)	Alcohol abstinence is recommended if there is current or previous history of excessive alcohol intake. (Strength of Evidence = C)	Deleted phrase discouraging alcohol use in ALVD. Other minor wording modifications.
5.4	It is recommended that all patients with ALVD with hypertension have aggressive blood pressure control. (Strength of Evidence = B)	It is recommended that all patients with ALVD with hypertension achieve optimal blood pressure control. (Strength of Evidence = B)	Aggressive blood pressure control changed to optimal blood pressure control
5.5	No changes		

5.6	ARBs are recommended for asymptomatic patients with reduced LVEF who are intolerant of ACE inhibitors because of cough or angioedema. (Strength of Evidence = C) Routine use of the combination of ACE inhibitors and ARBs for prevention of HF is not recommended in this population. (Strength of Evidence = C)	ARBs are recommended for asymptomatic patients with reduced LVEF who are intolerant of ACE inhibitors from cough or angioedema. (Strength of Evidence = C) Routine use of the combination of ACE inhibitors and ARBs for prevention of HF is not recommended in this population. (Strength of Evidence = C)	Minor wording modification
5.7	It is recommended that beta blocker therapy be administered to asymptomatic patients with reduced LVEF. (Post MI, Strength of Evidence = B; non–Post MI, Strength of Evidence = C)	Beta blocker therapy should be considered in asymptomatic patients with reduced LVEF. (post-MI, Strength of Evidence = B; non post-MI, Strength of Evidence = C)	Changed from ''is recommended'' to ''should be considered''
	Section 6: Nonpharmacologic Management and Health Care Maintenance in Patients with Chronic Heart Failure		
6.1	Dietary instruction regarding sodium intake is recommended in all patients with HF. Patients with HF and diabetes, dyslipidemia, or obesity should be given specific instructions regarding carbohydrate or caloric constraints. (Strength of Evidence = B)	Dietary instruction regarding sodium intake is recommended in all patients with HF. Patients with HF and diabetes, dyslipidemia, or severe obesity should be given specific dietary instructions. (Strength of Evidence = B)	Minor wording modification
6.2	No changes		
6.3	No changes		
6.4	It is recommended that specific attention be paid to nutritional management of patients with advanced HF and unintentional weight loss or muscle wasting (cardiac cachexia). Measurement of nitrogen balance, caloric intake, and prealbumin may be useful in determining appropriate nutritional supplementation. Caloric supplementation is recommended. Anabolic steroids are not recommended for such patients. (Strength of Evidence = C)	It is recommended that specific attention be paid to nutritional management of patients with advanced HF and unintentional weight loss or muscle wasting (cardiac cachexia). Measurement of nitrogen balance, caloric intake, and prealbumin may be useful in determining appropriate nutritional supplementation. Caloric supplementation is recommended. Anabolic steroids are not recommended for cachexic patients. (Strength of Evidence = C)	Minor wording modification
6.5	No changes		
6.6	Documentation of the type and dose of nutraceutical products used by patients with HF is recommended. (Strength of Evidence = C) Nutraceutical use is not recommended for relief of symptomatic HF or for the secondary prevention of cardiovascular events. Patients should be instructed to avoid using natural or synthetic products containing ephedra (ma huang), ephedrine, or its metabolites because of an increase risk of mortality and morbidity. Products should be avoided that may have significant drug interactions with digoxin, vasodilators, beta blockers, antiarrhythmic drugs, and anticoagulants. (Strength of Evidence = B)	Documentation of the type and dose of naturoceutical products used by patients with HF is recommended. (Strength of Evidence = C) Naturoceutical use is not recommended for relief of symptomatic HF or for the secondary prevention of cardiovascular events. Patients should be instructed to avoid using natural or synthetic products containing ephedra (ma huang), ephedrine, or its metabolites because of an increased risk of mortality and morbidity. Products should be avoided that may have significant drug interactions with digoxin, vasodilators, beta blockers, antiarrhythmic drugs, and anticoagulants. (Strength of Evidence = B)	Modification of terminology (nutraceutical to naturoceutical)
6.7	No changes		
6.8	No changes		
6.9	No changes		
6.10	It is recommended that screening for endogenous or prolonged reactive depression in patients with HF be conducted after diagnosis and at periodic intervals as clinically indicated. For pharmacologic treatment, selective serotonin receptor uptake inhibitors are preferred over tricyclic antidepressants, because the latter have the potential to cause ventricular arrhythmias, but the potential for drug interactions should be considered. (Strength of Evidence = B)	It is recommended that screening for endogenous or prolonged reactive depression in patients with HF be conducted following diagnosis and at periodic intervals as clinically indicated. For pharmacologic treatment, selective serotonin reuptake inhibitors are preferred over tricyclic antidepressants, because the latter have the potential to cause ventricular arrhythmias, but the potential for drug interactions should be considered. (Strength of Evidence = B)	Minor wording modification

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	2006 Guideline Recommendation	2010 Guideline Recommendation	Comments
6.11	No changes		
6.12	No changes		
6.13	No changes		
6.14	No changes		
6.15	Endocarditis prophylaxis is not recommended based on the diagnosis of HF alone. Prophylaxis for dental and other procedures should be given according to standard clinical indications. (Strength of Evidence = C)	Endocarditis prophylaxis is not recommended based on the diagnosis of HF alone. Consistent with the AHA recommendation, 'prophylaxis should be given for only specific cardiac conditions, associated with the highest risk of adverse outcome from endocarditis.' These conditions include: 'prosthetic cardiac valves; previous infective endocarditis; congenital heart disease (CHD)' such as: 'unrepaired cyanotic CHD, including palliative shunts and conduits; completely repaired congenital heart defect with prosthetic material or device, whether placed by surgery or by catheter intervention, during the first six months after the procedure; repaired CHD with residual defects at the site or adjacent to the site of a prosthetic patch or prosthetic device (which inhibit endothelialization); cardiac transplantation recipients who develop cardiac valvulopathy.' (Strength of Evidence = C)	Addition of criteria for endocarditis prophylaxis
6.16	No changes		
6.17	No changes		
6.18	No changes		
6.19		It is recommended that patients with HF undergo exercise testing to determine suitability for exercise training (patient does not develop significant ischemia or arrhythmias). (Strength of Evidence = B) If deemed safe, exercise training should be considered for patients with HF in order to facilitate understanding of exercise expectations (heart rate ranges and appropriate levels of exercise training), to increase exercise duration and intensity in a supervised setting, and to promote adherence to a general exercise goal of 30 minutes of moderate activity/exercise, 5 days per week with warm up and cool down exercises. (Strength of Evidence = B)	New recommendation
	Section 7: Heart Failure in Patients with Reduced Ejection Fraction		
7.1	No changes		
7.2	It is recommended that other therapy be substituted for ACE inhibitors in the following circumstances: • In patients who cannot tolerate ACE inhibitors because of cough, ARBs are recommended. (Strength of Evidence = A) • The combination of hydralazine and an oral nitrate may be considered in such patients not tolerating ARB therapy. (Strength of Evidence = C) • Patients intolerant to ACE inhibitors because of hyperkalemia or renal insufficiency are likely to experience the same side effects with ARBs. In these cases, the combination of hydralazine and an oral nitrate should be considered. (Strength of Evidence = C)	It is recommended that other therapy be substituted for ACE inhibitors in the following circumstances: • In patients who cannot tolerate ACE inhibitors due to cough, ARBs are recommended. (Strength of Evidence = A) • The combination of hydralazine and an oral nitrate may be considered in such patients not tolerating ARB therapy. (Strength of Evidence = C) • Patients intolerant to ACE inhibitors from hyperkalemia or renal insufficiency are likely to experience the same side effects with ARBs. In these cases, the combination of hydralazine and an oral nitrate should be considered. (Strength of Evidence = C)	Minor wording modification

7.3 (previous 7.10)	No changes		
7.4 (previous 7.12)	ARBs should be considered in patients experiencing angioedema while on ACE inhibitors based on their underlying risk and with recognition that angioedema has been reported infrequently with these agents. (Strength of Evidence = B) The combination of hydralazine and oral nitrates may be considered in this setting for patients who do not tolerate ARB therapy. (Strength of Evidence = C)	ARBs should be considered in patients experiencing angioedema while on ACE inhibitors based on their underlying risk and with recognition that angioedema has been reported infrequently with ARBs. (Strength of Evidence = B) The combination of hydralazine and oral nitrates may be considered in this setting for patients who do not tolerate ARB therapy. (Strength of Evidence = C)	Minor wording modifications
7.5 (previous 7.11)	Individual ARBs may be considered as initial therapy rather than ACE inhibitors for patients with the following conditions: • HF post MI (Strength of Evidence = A) • Chronic HF and systolic dysfunction (Strength of Evidence = B)	Individual ARBs may be considered as initial therapy rather than ACE inhibitors for patients with the following conditions: • HF Post-MI (Strength of Evidence = A) • Chronic HF and reduced LVEF (Strength of Evidence = B)	Terminology modification (changed "systolic dysfunction" to "reduced LVEF)
7.6 (previous 7.3)	No changes		
7.7 (previous 7.4)	No changes		
7.8 (previous 7.5)	Beta blocker therapy is recommended for patients with a recent decompensation of HF after optimization of volume status and successful discontinuation of intravenous diuretics and vasoactive agents, including inotropic support. Whenever possible, beta blocker therapy should be initiated in the hospital setting at a low dose before discharge in stable patients. (Strength of Evidence = B)	Beta blocker therapy is recommended for patients with a recent decompensation of HF after optimization of volume status and successful discontinuation of intravenous diuretics and vasoactive agents, including inotropic support. Whenever possible, beta blocker therapy should be initiated in the hospital setting at a low dose prior to discharge in stable patients. (Strength of Evidence = B)	Minor wording modifications
7.9 (previous 7.6)	Beta blocker therapy is recommended in the great majority of patients with LV systolic dysfunction, even if there is concomitant diabetes, chronic obstructive lung disease, or peripheral vascular disease. Beta blocker therapy should be used with caution in patients with diabetes with recurrent hypoglycemia, asthma, or resting limb ischemia. Considerable caution should be used if beta blockers are initiated in patients with marked bradycardia (<55 beats/min) or marked hypotension (systolic blood pressure <80 mm Hg). Beta blockers are not recommended in patients with asthma with active bronchospasm. (Strength of Evidence = C)	Beta blocker therapy is recommended in the great majority of patients with HF and reduced LVEF, even if there is concomitant diabetes, chronic obstructive lung disease, or peripheral vascular disease. Beta blocker therapy should be used with caution in patients with diabetes with recurrent hypoglycemia, with asthma, or with resting limb ischemia. Considerable caution should be used if beta blockers are initiated in patients with marked bradycardia (<55 beats/min) or marked hypotension (systolic blood pressure <80 mm Hg). Beta blockers are not recommended in patients with asthma with active bronchospasm. (Strength of Evidence = C)	Modification of terminology ("LV systolic dysfunction" changed to "reduced LVEF")
7.10 (previous 7.7)	It is recommended that b-blockade be initiated at low doses and uptitrated gradually, typically no sooner than at 2-week intervals. Doses found to be effective in HF trials generally are achieved in 8 to 12 weeks. Patients developing worsening HF symptoms or other side effects during titration may require a dosage adjustment of diuretic or concomitant vasoactive medications. If side effects resolve with medication adjustment, patients can subsequently be titrated to target or maximally tolerated doses. Some patients may require a more prolonged interval during uptitration, a temporary reduction in b-blocker dose, or, in rare cases, withdrawal of therapy. (Strength of Evidence = B)	It is recommended that beta blockade be initiated at low doses and uptitrated gradually, typically at 2-week intervals in patients with reduced LVEF, and after 3-10 day intervals in patients with reduced LVEF following newly diagnosed MI. (Strength of Evidence = B)	Deleted information related to beta blocker management

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	2006 Guideline Recommendation	2010 Guideline Recommendation	Comments
7.11 (previous 7.8)	It is recommended that beta blocker therapy be continued in most patients experiencing a symptomatic exacerbation of HF during chronic maintenance treatment. (Strength of Evidence = C) A temporary reduction of dose in this setting may be considered. Abrupt discontinuation in patients with symptomatic exacerbation should be avoided. (Strength of Evidence = C) If discontinued or reduced, beta blockers should be reinstated or the dose should be gradually increased before the patient is discharged.	It is recommended that beta blocker therapy be continued in most patients experiencing a symptomatic exacerbation of HF during chronic maintenance treatment, unless they develop cardiogenic shock, refractory volume overload, or symptomatic bradycardia (Strength of Evidence = C) A temporary reduction of dose (generally by one-half) in this setting may be considered. Abrupt discontinuation in patients with symptomatic exacerbation should be avoided, unless the situation is life-threatening. (Strength of Evidence = C) If discontinued or reduced, beta blockers should be reinstated before the patient is discharged. In general, doses should be uptitrated to the previous well-tolerated dose as soon as safely possible (Strength of Evidence =B)	Addition of criteria for beta blocker discontinuation and reinstitution
7.12 (previous 7.13)	The routine administration of an ARB is not recommended in addition to ACE inhibitor and beta blocker therapy in patients with recent acute MI and LV dysfunction. (Strength of Evidence = A)	The routine administration of an ARB is not recommended in addition to ACE inhibitor and beta blocker therapy in patients with a recent acute MI and reduced LVEF. (Strength of Evidence = A)	Modification of terminology (“LV dysfunction” changed to “reduced LVEF”)
7.13		The addition of an ARB should be considered in patients with HF due to reduced LVEF who have persistent symptoms or progressive worsening despite optimized therapy with an ACE inhibitor and beta blocker. (Strength of Evidence = A)	New recommendation
7.14	Administration of an aldosterone antagonist is recommended for patients with NYHA class IV or class III, previously class IV, HF from LV systolic dysfunction (LVEF ≤35%) while receiving standard therapy, including diuretics. (Strength of Evidence = A)	Administration of an aldosterone antagonist is recommended for patients with NYHA class IV (or class III, previously class IV) HF from reduced LVEF (<35%) while receiving standard therapy, including diuretics. (Strength of Evidence = A)	Modification of terminology (“LV systolic dysfunction” changed to “reduced LVEF”)
7.15	Administration of an aldosterone antagonist should be considered in patients after an acute MI, with clinical HF signs and symptoms and an LVEF <40%. Patients should be on standard therapy, including an ACE inhibitor (or ARB) and a b-blocker. (Strength of Evidence = A)	Administration of an aldosterone antagonist should be considered in patients following an acute MI, with clinical HF signs and symptoms or history of diabetes mellitus, and an LVEF <40%. Patients should be on standard therapy, including an ACE inhibitor (or ARB) and a beta blocker. (Strength of Evidence = A)	Addition of history of diabetes mellitus to criteria for therapy
7.16	No changes		
7.17	No changes		
7.18	No changes		
7.19	A combination of hydralazine and isosorbide dinitrate is recommended as part of standard therapy in addition to beta blockers and ACE inhibitors for African Americans with LV systolic dysfunction. • NYHA III or IV HF (Strength of Evidence = A) • NYHA II HF (Strength of Evidence = B) (See Section 15 Special Populations)	A combination of hydralazine and isosorbide dinitrate is recommended as part of standard therapy in addition to beta blockers and ACE inhibitors for African Americans with HF and reduced LVEF. • NYHA III or IV HF (Strength of Evidence = A) • NYHA II HF (Strength of Evidence = B) (See Section 15: Special Populations)	Modification of terminology (“LV systolic dysfunction” changed to “reduced LVEF”)
7.20	A combination of hydralazine and isosorbide dinitrate may be considered in non−African American patients with LV systolic dysfunction who remain symptomatic despite optimized standard therapy. (Strength of Evidence = C)	A combination of hydralazine and isosorbide dinitrate may be considered in non-African-American patients with HF and reduced LVEF who remain symptomatic despite optimized standard therapy. (Strength of Evidence = C)	Modification of terminology (“LV systolic dysfunction” changed to “reduced LVEF”)

7.21	Additional pharmacologic therapy should be considered in patients with HF due to systolic dysfunction who have persistent symptoms or progressive worsening despite optimized therapy with an ACE inhibitor and beta blocker. The choice of specific agent will be influenced by clinical considerations, including renal function status, chronic serum potassium concentration, blood pressure, and volume status. The triple combination of an ACE inhibitor, an ARB, and an aldosterone antagonist is not recommended because of the high risk of hyperkalemia. (Strength of Evidence = C) • Addition of an ARB. (Strength of Evidence = A) • Addition of an aldosterone antagonist: ○ For severe HF (Strength of Evidence = A) ○ For moderate HF (Strength of Evidence = C) • Addition of the combination of hydralazine/isosorbide dinitrate: ○ For African Americans (Strength of Evidence =A) ○ For others (Strength of Evidence = C)	Additional pharmacologic therapy should be considered in patients with HF and reduced LVEF who have persistent symptoms or progressive worsening despite optimized therapy with an ACE inhibitor and beta blocker. The choice of specific agent will be influenced by clinical considerations, including renal function status, chronic serum potassium concentration, blood pressure, and volume status. The triple combination of an ACE inhibitor, an ARB, and an aldosterone antagonist is not recommended because of the high risk of hyperkalemia. (Strength of Evidence = C) • Addition of an ARB. (Strength of Evidence = A) • Addition of an aldosterone antagonist: ○ for severe HF (Strength of Evidence =A) ○ for moderate HF (Strength of Evidence = C) ○ for post-MI HF (Strength of Evidence = A) • Addition of the combination of hydralazine/isosorbide dinitrate: ○ for African Americans (Strength of Evidence = A) ○ for others (Strength of Evidence = C)	Modification of terminology (“systolic dysfunction” changed to “reduced LVEF”); addition of post-MI HF under aldosterone antagonists
7.22	Additional pharmacological therapy should be considered in patients with HF due to systolic dysfunction who are unable to tolerate a beta blocker and have persistent symptoms or progressive worsening despite optimized therapy with an ACE inhibitor. The choice of specific agent will be influenced by clinical considerations, including renal function status, chronic serum potassium concentration, blood pressure and volume status. The triple combination of an ACE inhibitor, an ARB, and an aldosterone antagonist is not recommended due to the high risk of hyperkalemia. (Strength of Evidence = C) • Addition of an ARB. (Strength of Evidence = C) • Addition of an aldosterone antagonist: ○ for severe HF (Strength of Evidence = C) ○ for moderate HF (Strength of Evidence = C) • Addition of the combination of hydralazine/isosorbide dinitrate: ○ For African-Americans (Strength of Evidence = C) ○ for others (Strength of Evidence = C)	Additional pharmacological therapy should be considered in patients with HF and reduced LVEF *who are unable to tolerate a beta blocker* and have persistent symptoms or progressive worsening despite optimized therapy with an ACE inhibitor. The choice of specific agent will be influenced by clinical considerations, including renal function status, chronic serum potassium concentration, blood pressure and volume status. The triple combination of an ACE inhibitor, an ARB, and an aldosterone antagonist is not recommended due to the high risk of hyperkalemia. (Strength of Evidence = C) • Addition of an ARB. (Strength of Evidence = C) • Addition of an aldosterone antagonist: ○ for severe HF (Strength of Evidence = C) ○ for moderate HF (Strength of Evidence = C) • Addition of the combination of hydralazine/isosorbide dinitrate: ○ for African Americans (Strength of Evidence = C) ○ for others (Strength of Evidence = C)	Modification of terminology (“systolic dysfunction” changed to “reduced LVEF”)
7.23	No changes		
7.24	The initial dose of diuretic may be increased as necessary to relieve congestion. Restoration of normal volume status may require multiple adjustments over many days and occasionally weeks in patients with severe fluid overload evidenced by massive edema or ascites. After a diuretic effect is achieved with short acting loop diuretics, increasing administration frequency to twice or even 3 times per day will provide more diuresis with less physiologic perturbation than larger single doses. (Strength of Evidence = B) Oral torsemide may be considered in patients in whom poor absorption of oral medication or erratic diuretic effect may be present, particularly those with right-sided HF and refractory fluid retention despite high doses of other loop diuretics. (Strength of Evidence = C) Intravenous administration of diuretics may be necessary to relieve congestion. (Strength of Evidence = A) Diuretic refractoriness may represent patient noncompliance, a direct effect of diuretic use on the kidney, or progression of underlying cardiac dysfunction.	The initial dose of diuretic may be increased as necessary to relieve congestion. Restoration of normal volume status may require multiple adjustments over many days and occasionally weeks in patients with severe fluid overload evidenced by massive edema or ascites. After a diuretic effect is achieved with short-acting loop diuretics, increasing administration frequency to twice or even 3 times per day will provide more diuresis with less physiologic perturbation than larger single doses. (Strength of Evidence = B) Oral torsemide may be considered in patients in whom poor absorption of oral medication or erratic diuretic effect may be present, particularly those with right-sided HF and refractory fluid retention despite high doses of other loop diuretics. (Strength of Evidence = C) Intravenous administration of diuretics may be necessary to relieve congestion. (Strength of Evidence = A) Diuretic refractoriness may represent patient nonadherence, a direct effect of diuretic use on the kidney, or progression of underlying cardiac dysfunction.	Modification of terminology (“noncompliance” changed to “nonadherence”)

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Appendix A. (*continued*)

	2006 Guideline Recommendation	2010 Guideline Recommendation	Comments
7.25	No changes		
7.26	Careful observation for the development of side effects, including electrolyte abnormalities, symptomatic hypotension, and renal dysfunction, is recommended in patients treated with diuretics, especially when used at high doses and in combination. Patients should undergo routine laboratory studies and clinical examination as dictated by their clinical response. (Strength of Evidence = B)	Careful observation for the development of side effects, including electrolyte abnormalities, symptomatic hypotension, renal dysfunction, or worsening renal function, is recommended in patients treated with diuretics, especially when used at high doses and in combination. Patients should undergo routine laboratory studies and clinical examination as dictated by their clinical response. (Strength of Evidence = B)	Addition of worsening renal function to list of potential side effects
7.27	No changes		
7.28	No changes		
7.29	Digoxin should be considered for patients with LV systolic dysfunction (LVEF ≤40%) who have signs or symptoms of HF while receiving standard therapy, including ACE inhibitors and beta blockers: NYHA class II-III (Strength of Evidence = A) NYHA class IV (Strength of Evidence = B)	Digoxin may be considered to improve symptoms in patients with reduced LVEF (LVEF ≤40%) who have signs or symptoms of HF while receiving standard therapy, including ACE inhibitors and beta blockers: • NYHA class II-III (Strength of Evidence = B) • NYHA class IV (Strength of Evidence = C)	Modification from "should be considered" to "may be considered", and change in Strength of Evidence
7.30	It is recommended that the dose of digoxin, which should be based on lean body mass, renal function and concomitant medications, should be 0.125 mg daily in the majority of patients and the serum digoxin level should be <1.0 ng/mL. (Strength of Evidence = C)	It is recommended that the dose of digoxin, which should be based on lean body mass, renal function, and concomitant medications, should be 0.125 mg daily in the majority of patients and the serum digoxin level should be <1.0 ng/mL, generally 0.7-0.9 ng/mL. (Strength of Evidence = B)	Addition of a lower serum concentration range (0.7-0.9 ng/ml), and change in strength of evidence from C to B
7.31	Adequate control of the ventricular response to atrial fibrillation in patients with HF is recommended. (Level of Evidence = B)	Digoxin should be considered for achieving adequate control of the ventricular response to atrial fibrillation in patients with HF. (Strength of Evidence = B)	Modification from "is recommended" to "should be considered"
7.32	No changes		
7.33	Treatment with warfarin (goal INR 2.0−3.0) is recommended for all patients with HF and chronic or documented paroxysmal atrial fibrillation (Strength of Evidence = A) or a history of systemic or pulmonary emboli, including stroke or transient ischemic attack, (Strength of Evidence = C) unless contraindicated.	Treatment with warfarin (goal international normalized ratio [INR] 2.0-3.0) is recommended for all patients with HF and chronic or documented paroxysmal, persistent, or long-standing atrial fibrillation (Strength of Evidence = A) or a history of systemic or pulmonary emboli, including stroke or transient ischemic attack (Strength of Evidence = C), unless contraindicated.	Addition of persistent or long-standing atrial fibrillation
7.34	No changes		
Previous 7.35			Deleted from current guideline
7.35 (previous 7.36)	Long-term treatment with an antithrombotic agent is recommended for patients with HF from ischemic cardiomyopathy, whether or not they are receiving ACE inhibitors. (Strength of Evidence = B) Aspirin is recommended in most patients for whom anticoagulation is not specifically indicated because of its proven efficacy in non-HF patients with ischemic heart disease, its convenience, and lower cost. Lower doses of aspirin (75 or 81 mg) may be preferable because data from 2 trials suggest more frequent worsening of HF at higher doses. (Strength of Evidence = C) Warfarin (goal INR 2.0−3.5) and clopidogrel (75 mg) have also prevented vascular events in post MI patients and may be considered as alternatives to aspirin. (Strength of Evidence = B)	Long-term treatment with an antiplatelet agent, generally aspirin in doses of 75 to 81 mg, is recommended for patients with HF due to ischemic cardiomyopathy, whether or not they are receiving ACE inhibitors. (Strength of Evidence = B) Warfarin (goal INR 2.0-3.0) and clopidogrel (75 mg) also have prevented vascular events in post-MI patients and may be considered as alternatives to aspirin. (Strength of Evidence = B)	Modification of terminology from "antithrombotic" to "antiplatelet"; addition of recommended doses for aspirin. INR range changed to 2.0-3.0

7.36 (previous 7.37)	Routine use of aspirin is not recommended in patients with HF not from ischemic cardiomyopathy and without other evidence of atherosclerotic vascular disease. (Strength of Evidence = C)	Routine use of aspirin is not recommended in patients with HF without atherosclerotic vascular disease. (Strength of Evidence = C)	Modification of terminology
Previous 7.38			Deleted from current guideline; addressed in recommendation 7.35
7.37 (previous 7.39)	No changes		
7.38 (previous 7.40)	In patients with HF and an implantable cardioverter defibrillator (ICD), amiodarone may be considered to reduce the frequency of repetitive discharges. (Strength of Evidence = C)	In patients with HF and an ICD, amiodarone may be considered to reduce the frequency of recurrent symptomatic arrhythmias causing ICD shocks. (Strength of Evidence = C)	Modification of wording
7.39 (previous 7.41)	It is recommended that patients taking amiodarone therapy and digoxin or warfarin generally have their maintenance doses of many commonly used agents, such as digoxin, warfarin, and statins, reduced when amiodarone is initiated and then carefully monitored for the possibility of adverse drug interactions. Adjustment in doses of these drugs and laboratory assessment of drug activity or serum concentration after initiation of amiodarone is recommended. (Strength of Evidence = A)	It is recommended that when amiodarone therapy is initiated, the potential for interactions with other drugs be reviewed. The maintenance doses of digoxin, warfarin, and some statins should be reduced when amiodarone is initiated and then carefully monitored. Adjustment in doses of these drugs and laboratory assessment of drug activity or serum concentration after initiation of amiodarone is recommended. (Strength of Evidence = A)	Modification of wording
7.40		Routine use of amiodarone therapy for asymptomatic arrhythmias that are not felt to contribute to HF or ventricular dysfunction is not recommended. (Strength of Evidence = B)	New recommendation
7.41		n-3 polyunsaturated fatty acids (PUFA) may be considered to reduce mortality in HF patients with NYHA class II-IV symptoms and reduced LVEF. (Strength of Evidence = B)	New recommendation
	Section 8: Disease Management, Advance Directives, and End-of-Life Care in Heart Failure		
8.1	It is recommended that patients with HF and their family members or caregivers receive individualized education and counseling that emphasizes self-care. This education and counseling should be delivered by providers using a team approach in which nurses with expertise in HF management provide the majority of education and counseling, supplemented by physician input and, when available and needed, input from dietitians, pharmacists, and other health care providers. All HF patients benefit from education and counseling, but patients in NYHA functional class III or IV need the most intensive education, whereas patients in NYHA I or II need less intensive education. (Strength of Evidence = B) Teaching is not sufficient without skill building and specification of critical target behaviors. Essential elements of patient education to promote self-care with associated skills are shown in Table 8.1. (Strength of Evidence = B)	It is recommended that patients with HF and their family members or caregivers receive individualized education and counseling that emphasizes self-care. This education and counseling should be delivered by providers using a team approach in which nurses with expertise in HF management provide the majority of education and counseling, supplemented by physician input and, when available and needed, input from dietitians, pharmacists, and other health care providers. (Strength of Evidence = B) Teaching is not sufficient without skill building and specification of critical target behaviors. It is recommended that essential elements of patient education (with associated skills) are utilized to promote self-care as shown in Table 8.1. (Strength of Evidence = B)	Deletion of NYHA specific portion of the recommendation; modification of wording

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Appendix A. (*continued*)

	2006 Guideline Recommendation	2010 Guideline Recommendation	Comments
8.2	It is recommended that patients' literacy, cognitive status, psychologic state, culture, and access to social and financial resources be taken into account for optimal education and counseling. Because cognitive impairment and depression are common in HF and can seriously interfere with learning, patients should be screened for these. Appropriate interventions, such as supportive counseling and pharmacotherapy, are recommended for those patients found to be depressed. Patients found to be cognitively impaired need additional support to manage their HF. (Strength of Evidence = C)	It is recommended that patients' literacy, cognitive status, psychological state, culture, and access to social and financial resources be taken into account for optimal education and counseling. Because cognitive impairment and depression are common in HF and can seriously interfere with learning, patients should be screened for these. Patients found to be cognitively impaired need additional support to manage their HF. (Strength of Evidence = B)	Deletion of description of interventions; modification of Strength of Evidence from C to B
8.3	No changes		
8.4	It is recommended that the frequency and intensity of patient education and counseling vary according to the stage of illness. Patients in advanced HF or with persistent difficulty adhering to the recommended regimen require the most eduction and counseling. Patients should be offered a variety of options for learning about HF according to their individual preferences: videotape, one-on-one or group discussion, reading materials, translators, telephone calls, mailed information, internet, visits. Repeated exposure to material is essential because a single session is never sufficient. (Strength of Evidence = B)	It is recommended that the frequency and intensity of patient education and counseling vary according to the stage of the illness. Patients in advanced HF or persistent difficulty adhering to the recommended regimen require the most education and counseling. Patients should be offered a variety of options for learning about HF according to their individual preferences: videotape, one-on-one or group discussion, reading materials, translators, telephone calls, mailed information, internet, visits. Repeated exposure to material is recommended because a single session is never sufficient. (Strength of Evidence = B)	Modification of wording
8.5	No changes		
8.6	No changes		
8.7	Patients recently hospitalized for HF and other patients at high risk should be considered for referral to a comprehensive HF disease management program that delivers individualized care. High-risk patients include those with renal insufficiency, low output state, diabetes, chronic obstructive pulmonary disease, persistent NYHA class III or IV symptoms, frequent hospitalization for any cause, multiple active comorbidities, or a history of depression, cognitive impairment, or persistent nonadherence to therapeutic regimens. (Strength of Evidence = A)	Patients recently hospitalized for HF and other patients at high risk for HF decompensation should be considered for comprehensive HF disease management. High-risk patients include those with renal insufficiency, low output state, diabetes, chronic obstructive pulmonary disease, persistent NYHA class III or IV symptoms, frequent hospitalization for any cause, multiple active comorbidities, or a history of depression, cognitive impairment, inadequate social support, poor health literacy, or persistent nonadherence to therapeutic regimens. (Strength of Evidence = A)	Addition of poor health literacy
8.8	No changes		
8.9	No changes		
8.10	No changes		
8.11	Patient and family or caregiver discussions about quality of life and prognosis are recommended as part of the disease management of HF. (Strength of Evidence = C)	It is recommended that patient and family or caregiver discussions about quality of life and prognosis be included in the disease management of HF. (Strength of Evidence = C)	Modification of wording

8.12	It is recommended that the patient's status be optimized medically and psychologically before discussing the possibility that end-of-life care is indicated. The decision to declare a patient as an appropriate candidate for end-of-life care should be made by physicians experienced in the care of patients with HF. End-of-life management should be coordinated with the patient's primary care physician. As often as possible, discussions regarding end-of-life care should be initiated while the patient is still capable of participating in decision making. (Strength of Evidence = C)	It is recommended that • Seriously ill patients with HF and their families be educated to understand that patients with HF are at high risk of death, even while aggressive efforts are made to prolong life. • Patients with HF be made aware that HF is potentially life-limiting, but that pharmacologic and device therapies and self-management can prolong life. In most cases, chronic HF pharmacologic and device therapies should be optimized as indicated before identifying that patients are near end-of-life. • Identification of end-of-life in a patient should be made in collaboration with clinicians experienced in the care of patients with HF when possible. • End-of-life management should be coordinated with the patient's primary care physician. • As often as possible, discussions regarding end-of-life care should be initiated while the patient is still capable of participating in decision-making. (Strength of Evidence = C)	Addition of criteria for end of life care
8.13	End-of-life care should be considered in patients who have advanced, persistent HF with symptoms at rest despite repeated attempts to optimize pharmacologic and nonpharmacologic therapy, as evidenced by one or more of the following: • Frequent hospitalizations (3 or more per year) • Chronic poor quality of life with inability to accomplish activities of daily living • Need for intermittent or continuous intravenous support • Consideration of assist devices as destination therapy (Strength of Evidence = C)	End-of-life care should be considered in patients who have advanced, persistent HF with symptoms at rest despite repeated attempts to optimize pharmacologic, cardiac device, and other therapies, as evidenced by 1 or more of the following: • HF hospitalization (Strength of Evidence = B) • Chronic poor quality of life with minimal or no ability to accomplish activities of daily living (Strength of Evidence = C) • Need for continuous intravenous inotropic therapy support (Strength of Evidence = B)	Addition of cardiac device to list of optimization therapies; modification of strength of evidence
8.14	It is recommended that end-of-life care strategies be individualized, include effective symptom management, and avoid unnecessary testing and interventions. (Strength of Evidence = C)	It is recommended that end-of-life care strategies be individualized and include core HF pharmacologic therapies, effective symptom management and comfort measures, while avoiding unnecessary testing. New life-prolonging interventions should be discussed with patients and care-givers with careful discussion of whether they are likely to improve symptoms. (Strength of Evidence = C)	Addition of information regarding end-of-life care strategies
8.15	It is recommended that, as part of end-of life-care, patients and their families/caregivers be given specific directions concerning their response to clinical events if they decide against resuscitation. Inactivation of an implantable defibrillation device should be discussed. (Strength of Evidence = C)	It is recommended that a specific discussion about resuscitation be held in the context of planning for overall care and for emergencies with all patients with HF. The possibility of SCD for patients with HF should be acknowledged. Specific plans to reduce SCD (for example with an ICD) or to allow natural death should be based on the individual patient's risks and preferences for an attempt at resuscitation with specific discussion of risks and benefits of inactivation the ICD. Preferences for attempts at resuscitation and plans for approach to care should be readdressed at turning points in the patient's course or if potentially life-prolonging interventions are considered. (Strength of Evidence = C)	Addition of information regarding resuscitation
8.16		It is recommended that, as part of end-of-life care, patients and their families/caregivers have a plan to manage a sudden decompensation, death, or progressive decline. Inactivation of an implantable defibrillation device should be discussed in the context of allowing natural death at end of life. A process for deactivating defibrillators should be clarified in all settings in which patients with HF receive care. (Strength of Evidence = C)	New recommendation

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Appendix A. (*continued*)

	2006 Guideline Recommendation	2010 Guideline Recommendation	Comments
8.17	Patients with HF undergoing end-of-life care may be considered for hospice services that can be delivered in the home, a hospital setting, or a special hospice unit. (Strength of Evidence = C)	Patients with HF receiving end-of-life care should be considered for enrollment in hospice that can be delivered in the home, a nursing home, or a special hospice unit. (Strength of Evidence = C)	Modification from "may be considered" to "should be considered"
Previous 8.16 and 8.18			Deleted recommendations; portions of these recommendations have been incorporated into recommendations 8.15 and 8.16
	Section 9: Electrophysiology Testing and the Use of Devices in Heart Failure		
9.1	It is recommended that the decision to undertake electrophysiologic intervention be made in light of functional status and prognosis based on severity of underlying HF and comorbid conditions. If LV dysfunction is a reason for recommending electrophysiologic intervention, LV function should be re-assessed, ideally after 3−6 months of optimal medical therapy. (Strength of Evidence = C)	It is recommended that the decision to undertake electrophysiologic intervention, including ICD implantation, be made in light of functional status and prognosis based on severity of underlying HF and comorbid conditions. If an ICD is considered due to LV dysfunction which is of recent onset, LV function should be reassessed, ideally after 3-6 months of optimal medical therapy. (Strength of Evidence = C)	Modification/clarification of wording
9.2	Immediate evaluation is recommended in patients with HF who present with syncope. In the absence of a clear identifiable noncardiac cause, patients should be referred for electrophysiologic evaluation. (Strength of Evidence = C)	Immediate evaluation is recommended in patients with HF who present with syncope. In the absence of a clear identifiable noncardiac cause, consultation with an EP specialist should be obtained. (Strength of Evidence = C)	Modification/clarification of wording
9.3	No changes		
9.4	In patients with or without concomitant coronary artery disease (including a prior MI >1 month ago): a) Prophylactic ICD placement should be considered (LVEF ≤30%) and may be considered (LVEF 31−35%) for those with mild to moderate HF symptoms (NYHA II-III). (Strength of Evidence = A) See Recommendation 9.1 for additional criteria. b) Concomitant ICD placement should be considered in patients undergoing implantation of a biventricular pacing device according to the criteria in Recommendations 9.7−9.8. (Strength of Evidence = B) See Recommendation 9.1 for additional criteria.	a. Prophylactic ICD placement should be considered in patients with an LVEF ≤35% and mild to moderate HF symptoms: • Ischemic etiology (Strength of Evidence = A) • Non-ischemic etiology (Strength of Evidence = B) See Recommendation 9.1 for additional criteria. b. In patients who are undergoing implantation of a biventricular pacing device according to the criteria in recommendations 9.7-9.8, use of a device that provides defibrillation should be considered. (Strength of Evidence = B) See Recommendation 9.1 for additional criteria.	Revision of LVEF criteria and strength of evidence based on etiology
9.5	ICD placement is not recommended in chronic, severe refractory HF when there is no reasonable expectation for improvement. (Strength of Evidence = C)	ICD placement is not recommended in chronic, severe refractory HF when there is no reasonable expectation for improvement or in patients with a life expectancy of less than 1 year. (Strength of Evidence = C)	Addition of life expectancy criterion to recommendation
9.6	ICD implantation is recommended for survivors of cardiac arrest from ventricular fibrillation or hemodynamically unstable sustained ventricular tachycardia without evidence of acute MI or if the event occurs more than 48 hours after the onset of infarction in the absence of a recurrent ischemic event. (Strength of Evidence = A)	ICD implantation is recommended for survivors of cardiac arrest from ventricular fibrillation or hemodynamically unstable sustained VT that is not due to a transient, potentially reversible cause, such as acute MI. (Strength of Evidence = A)	Revision of MI criteria
9.7	Biventricular pacing therapy should be considered for patients with sinus rhythm, a widened QRS interval (≥120 ms) and severe LV systolic dysfunction (LVEF ≤35% with LV dilatation >5.5 cm) who have persistent, moderate to severe HF (NYHA III) despite optimal medical therapy. (Strength of Evidence = A)	Biventricular pacing therapy is recommended for patients in sinus rhythm with a widened QRS interval (≥120 ms) and severe LV systolic dysfunction LVEF (≤ 35%) who have persistent, moderate to severe HF (NYHA III) despite optimal medical therapy. (Strength of Evidence = A)	Modification from "should be considered" to "is recommended"; removal of LV dimension criterion

9.8		Biventricular pacing therapy may be considered for patients with atrial fibrillation with a widened QRS interval (≥120 ms) and severe LV systolic dysfunction LVEF ≤35% who have persistent, moderate to severe HF (NYHA III) despite optimal medical therapy. (Strength of Evidence = B)	New recommendation
9.9 (Previous 9.8)	Selected ambulatory NYHA IV patients may be considered for biventricular pacing therapy. (Strength of Evidence = B)	Selected ambulatory NYHA IV patients in sinus rhythm with QRS ≥ 120 ms and LV systolic dysfunction may be considered for biventricular pacing therapy. (Strength of Evidence = B)	Additional criteria for patient selection
9.10 (previous 9.9)	Biventricular pacing therapy is not recommended in patients who are asymptomatic or have mild HF symptoms. (Strength of Evidence = C)	Biventricular pacing therapy may be considered in patients with reduced LVEF and QRS ≥ 150 ms who have NYHA I or II HF symptoms. (Strength of Evidence = B)	Modification from "is not recommended" to "may be considered"; modification of strength of evidence from C to B; additional criteria for patient selection
9.11		In patients with reduced LVEF who require chronic pacing and in whom frequent ventricular pacing is expected, biventricular pacing may be considered. (Strength of Evidence = C)	New recommendation
9.12 (previous 9.10)	No changes		
	Section 10: Surgical Approaches to the Treatment of Heart Failure		
10.1	No changes		
10.2	No changes		
10.3	No changes		
10.4	No changes		
10.5	No changes		
10.6	No changes		
10.7		Patients with refractory HF and hemodynamic instability, and/or compromised end-organ function, with relative contraindications to cardiac transplantation or permanent mechanical circulatory assistance expected to improve with time or restoration of an improved hemodynamic profile should be considered for urgent mechanical circulatory support as a "bridge to decision." These patients should be referred to a center with expertise in the management of patients with advanced HF. (Strength of Evidence = C)	New recommendation
	Section 11: Evaluation and Management of Patients with Heart Failure and Preserved LVEF		
11.1	Careful attention to differential diagnosis is recommended in patients with HF and preserved LVEF to distinguish among a variety of cardiac disorders, because treatments may differ. These various entities may be distinguished based on echocardiography, electrocardiography, and stress imaging (via exercise or pharmacologic means using myocardial perfusion or echocardiographic imaging). See algorithm in Figure 11.1 for a detailed approach to differential diagnosis. (Strength of Evidence = C)	Careful attention to differential diagnosis is recommended in patients with HF and preserved LVEF to distinguish among a variety of cardiac disorders, because treatments may differ. These various entities may be distinguished based on echocardiography, electrocardiography, and stress imaging (via exercise or pharmacologic means, using myocardial perfusion or echocardiographic imaging) and cardiac catheterization. See Figures 11.1, 11.2, and 11.3 for guidance to a differential diagnosis. (Strength of Evidence = C)	Addition of cardiac catheterization to list of diagnostic tools, modification of Figure 11.3 and addition of Figures 11.1 and 11.2.

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	2006 Guideline Recommendation	2010 Guideline Recommendation	Comments
11.2	Evaluation for the possibility of ischemic heart disease and inducible myocardial ischemia is recommended in patients with HF and preserved LVEF. (Strength of Evidence = C)	Evaluation for ischemic heart disease and inducible myocardial ischemia is recommended in patients with HF and preserved LVEF (see Section 13). (Strength of Evidence = C)	Minor wording modifications
11.3	Aggressive blood pressure management is recommended in patients with HF and preserved LVEF (Section 14, Recommendation 14.15). (Strength of Evidence = C)	Blood pressure monitoring is recommended in patients with HF and preserved LVEF (Section 14, Recommendation 14.1). (Strength of Evidence = C)	Modification of terminology (“aggressive blood pressure management” changed to “blood pressure monitoring”)
11.4	No changes		
11.5	No changes		
11.6	ARBs or ACE inhibitors should be considered in patients with HF and preserved LVEF. (Strength of evidence = B) • ARBs (Strength of Evidence = B) • ACE inhibitors (Strength of Evidence = C)	In the absence of other specific indications for these drugs, ARBs or ACE inhibitors may be considered in patients with HF and preserved LVEF. • ARBs (Strength of Evidence = C) • ACE inhibitors (Strength of Evidence = C)	Modification from “should be considered” to “may be considered”; modification of strength of evidence for ARBs from B to C
11.7	No changes		
11.8	No changes		
11.9	Calcium channel blockers should be considered in patients with: • Atrial fibrillation requiring control of ventricular rate in whom b-blockers have proven inadequate for this purpose because of intolerance. In these patients, diltiazem or verapamil should be considered. (Strength of Evidence = C) • Symptom-limiting angina. (Strength of Evidence = A) • Hypertension. Amlodipine should be considered. (Strength of Evidence = C)	Calcium channel blockers should be considered in patients with HF and preserved LVEF and: • Atrial fibrillation requiring control of ventricular rate and intolerance to beta blockers. In these patients, diltiazem or verapamil should be considered. (Strength of Evidence = C) • Symptom-limiting angina. (Strength of Evidence = A) • Hypertension. (Strength of Evidence = C)	Modification of wording regarding beta blocker intolerance
11.10	Measures to restore and maintain sinus rhythm should be considered in patients who have symptomatic atrial flutter-fibrillation, but this decision should be individualized. (Strength of Evidence = C)	Measures to restore and maintain sinus rhythm may be considered in patients who have symptomatic atrial flutter-fibrillation and preserved LVEF, but this decision should be individualized. (Strength of Evidence = C)	Modification from “should be considered” to “may be considered”
	Section 12: Evaluation and Management of Patients with Acute Decompensated Heart Failure		
12.1	The diagnosis of decompensated HF should be based primarily on signs and symptoms. (Strength of Evidence = C) When the diagnosis is uncertain, determination of BNP or NT-proBNP concentration should be considered in patients being evaluated for dyspnea who have signs and symptoms compatible with HF. (Strength of Evidence = A) 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.	The diagnosis of ADHF should be based primarily on signs and symptoms. (Strength of Evidence = C) When the diagnosis is uncertain, determination of BNP or NT-proBNP concentration is recommended in patients being evaluated for dyspnea who have signs and symptoms compatible with HF. (Strength of Evidence = A) 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, and with the knowledge of cardiac and non-cardiac factors that can raise or lower natriuretic peptide levels.	Modification of BNP recommendation from “should be considered” to “is recommended”
12.2	No changes		

12.3	No changes		
12.4	No changes		
12.5	No changes		
12.6	It is recommended that diuretics be administered at doses needed to produce a rate of diuresis sufficient to achieve optimal volume status with relief of signs and symptoms of congestion (edema, elevated JVP, dyspnea), without inducing an excessively rapid reduction in intravascular volume, which may result in symptomatic hypotension and/or worsening renal function. (Strength of Evidence = C)	It is recommended that diuretics be administered at doses needed to produce a rate of diuresis sufficient to achieve optimal volume status with relief of signs and symptoms of congestion (edema, elevated JVP, dyspnea), without inducing an excessively rapid reduction in 1) intravascular volume, which may result in symptomatic hypotension and/or worsening renal function, or 2) serum electrolytes, which may precipitate arrhythmias or muscle cramps. (Strength of Evidence = C)	Addition of serum electrolytes
12.7	No changes		
12.8	Monitoring of daily weights, intake, and output is recommended to assess clinical efficacy of diuretic therapy. Routine use of a Foley catheter is not recommended for monitoring volume status. However, placement of a catheter is recommended when close monitoring of urine output is needed. (Strength of Evidence = C)	Monitoring of daily weights, intake, and output is recommended to assess clinical efficacy of diuretic therapy. Routine use of a Foley catheter is not recommended for monitoring volume status. However, placement of a catheter is recommended when close monitoring of urine output is needed or if a bladder outlet obstruction is suspected of contributing to worsening renal function. (Strength of Evidence = C)	Addition of criterion for catheter placement
12.9	Careful observation for development of a variety of side effects, including renal dysfunction, electrolyte abnormalities and symptomatic hypotension, is recommended in patients treated with diuretics, especially when used at high doses and in combination. Patients should undergo routine laboratory studies and clinical examination as dictated by their clinical response. (Strength of Evidence = C) Serum potassium and magnesium levels should be monitored at least daily and maintained in the normal range. More frequent monitoring may be necessary when diuresis is rapid. (Strength of Evidence = C) Overly rapid diuresis may be associated with severe muscle cramps, which should be treated with potassium replacement if indicated. (Strength of Evidence = C)	Careful observation for development of a variety of side effects, including renal dysfunction, electrolyte abnormalities, symptomatic hypotension, and gout is recommended in patients treated with diuretics, especially when used at high doses and in combination. Patients should undergo routine laboratory studies and clinical examination as dictated by their clinical response. (Strength of Evidence = C) It is recommended that serum potassium and magnesium levels should be monitored at least daily and maintained in the normal range. More frequent monitoring may be necessary when diuresis is rapid. (Strength of Evidence = C) Overly rapid diuresis may be associated with severe muscle cramps. If indicated, treatment with potassium replacement is recommended. (Strength of Evidence = C)	Addition of gout as side effect Wording modified
12.10	No changes		
12.11	When congestion fails to improve in response to diuretic therapy, the following options should be considered: • Sodium and fluid restriction, • Increased doses of loop diuretic, • Continuous infusion of a loop diuretic, or • Addition of a second type of diuretic orally (metolazone or spironolactone) or intravenously (chlorothiazide). • A fifth option, ultrafiltration, may be considered. (Strength of Evidence = C)	When congestion fails to improve in response to diuretic therapy, the following options should be considered: • Re-evaluating presence/absence of congestion • Sodium and fluid restriction, • Increasing doses of loop diuretic, • Continuous infusion of a loop diuretic, or • Addition of a second type of diuretic orally (metolazone or spironolactone) or intravenously (chlorothiazide). Another option, ultrafiltration, may be considered. (Strength of Evidence = C)	Addition of re-evaluation of congestion
12.12	A low-sodium diet (2 g daily) is recommended, as is supplemental oxygen, as needed for hypoxemia. (Strength of Evidence = C) In patients with recurrent or refractory volume overload, stricter sodium restriction may be considered. (Strength of Evidence = C)	A low sodium diet (2 g daily) is recommended for most hospitalized patients. (Strength of Evidence = C) In patients with recurrent or refractory volume overload, stricter sodium restriction may be considered. (Strength of Evidence = C)	Deletion of supplemental oxygen (moved to recommendation 12.14)

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	2006 Guideline Recommendation	2010 Guideline Recommendation	Comments
12.13	No changes		
12.14	Routine administration of supplemental oxygen in the absence of hypoxia is not recommended. (Strength of Evidence = C)	Routine administration of supplemental oxygen in the presence of hypoxia is recommended. (Strength of Evidence = C) Routine administration of supplemental oxygen in the absence of hypoxia is not recommended. (Strength of Evidence = C)	Addition of recommendation for oxygen in the presence of hypoxemia
12.15		Use of non-invasive positive pressure ventilation may be considered for severely dyspneic patients with clinical evidence of pulmonary edema. (Strength of Evidence = A)	New recommendation
12.16		Venous thromboembolism prophylaxis with low dose unfractionated heparin, low molecular weight heparin, or fondaparinux to prevent proximal deep venous thrombosis and pulmonary embolism is recommended for patients who are admitted to the hospital with ADHF and who are not already anticoagulated and have no contraindication to anticoagulation. (Strength of Evidence = B) Venous thromboembolism prophylaxis with a mechanical device (intermittent pneumatic compression devices or graded compression stockings) to prevent proximal deep venous thrombosis and pulmonary embolism should be considered for patients who are admitted to the hospital with ADHF and who are not already anticoagulated and who have a contraindication to anticoagulation. (Strength of Evidence = C)	New recommendation
12.17 (previous 12.15)	In the absence symptomatic hypotension, intravenous nitroglycerin, nitroprusside, or nesiritide may be considered as an addition to diuretic therapy for rapid improvement of congestive symptoms in patients admitted with ADHF. Frequent blood pressure monitoring is recommended with these agents. (Strength of Evidence = B). These agents should be decreased in dosage on discontinued if symptomatic hypotension develops. (Strength of Evidence = B) Reintroduction in increasing doses may be considered once symptomatic hypotension is resolved. (Strength of Evidence = C)	In the absence of symptomatic hypotension, intravenous nitroglycerin, nitroprusside or nesiritide may be considered as an addition to diuretic therapy for rapid improvement of congestive symptoms in patients admitted with ADHF. (Strength of Evidence = B) Frequent blood pressure monitoring is recommended with these agents. (Strength of Evidence = B) These agents should be decreased in dosage or discontinued if symptomatic hypotension or worsening renal function develops. (Strength of Evidence = B) Reintroduction in increasing doses may be considered once symptomatic hypotension is resolved. (Strength of Evidence = C)	Addition of worsening renal function as potential side effect
12.18 (previous 12.16)	No changes		
12.19 (previous 12.17)	Intravenous vasodilators (nitroprusside, nitroglycerin, or nesiritide) may be considered in patients with ADHF and advanced HF who have persistent severe HF despite aggressive treatment with diuretics and standard oral therapies. (Strength of Evidence = C)	Intravenous vasodilators (nitroprusside, nitroglycerin, or nesiritide) may be considered in patients with ADHF who have persistent severe HF despite aggressive treatment with diuretics and standard oral therapies. • Nitroprusside (Strength of Evidence = B) • Nitroglycerine, Nesiritide (Strength of Evidence = C)	Modification of strength of evidence for nitroprusside from C to B

12.20 (previous 12.18)	Intravenous inotropes (milrinone or dobutamine) may be considered to relieve symptoms and improve end-organ function in patients with advanced HF characterized by LV dilation, reduced LVEF, and diminished peripheral perfusion or end-organ dysfunction (low output syndrome), particularly if these patients have marginal systolic blood pressure (<90 mm Hg), have symptomatic hypotension despite adequate filling pressure, or are unresponsive to, or intolerant of, intravenous vasodilators. (Strength of Evidence = C) These agents may be considered in similar patients with evidence of fluid overload if they respond poorly to intravenous diuretics or manifest diminished or worsening renal function. (Strength of Evidence = C) When adjunctive therapy is needed in other patients with ADHF, administration of vasodilators should be considered instead of intravenous inotropes (milrinone or dobutamine). (Strength of Evidence = B) Intravenous inotropes (milrinone or dobutamine) are not recommended unless left heart filling pressures are known to be elevated based on direct measurement or clear clinical signs. (Strength of Evidence = B) Administration of intravenous inotropes (milrinone or dobutamine) in the setting of ADHF should be accompanied by continuous or frequent blood pressure monitoring and continuous monitoring of cardiac rhythm. (Strength of Evidence = C) If symptomatic hypotension or worsening tachyarrhythmias develop during administration of these agents, discontinuation or dose reduction should be considered. (Strength of Evidence = C)	Intravenous inotropes (milrinone or dobutamine) may be considered to relieve symptoms and improve end-organ function in patients with advanced HF characterized by LV dilation, reduced LVEF, and diminished peripheral perfusion or end-organ dysfunction (low output syndrome), particularly if these patients have marginal systolic blood pressure (< 90 mm Hg), have symptomatic hypotension despite adequate filling pressure, or are unresponsive to, or intolerant of, intravenous vasodilators. (Strength of Evidence = C) These agents may be considered in similar patients with evidence of fluid overload if they respond poorly to intravenous diuretics or manifest diminished or worsening renal function. (Strength of Evidence = C) When adjunctive therapy is needed in other patients with ADHF, administration of vasodilators should be considered instead of intravenous inotropes (milrinone or dobutamine). (Strength of Evidence = C) Intravenous inotropes (milrinone or dobutamine) are not recommended unless left heart filling pressures are known to be elevated or cardiac index is severely impaired based on direct measurement or clear clinical signs. (Strength of Evidence = C) It is recommended that administration of intravenous inotropes (milrinone or dobutamine) in the setting of ADHF be accompanied by continuous or frequent blood pressure monitoring and continuous monitoring of cardiac rhythm. (Strength of Evidence = C) If symptomatic hypotension or worsening tachyarrhythmias develop during administration of these agents, discontinuation or dose reduction should be considered. (Strength of Evidence = C)	Modification of strength of evidence from B to C for portions of this recommendation Wording modified
12.21 (previous 12.19)	No changes		
12.22 (previous 12.20)	Invasive hemodynamic monitoring should be considered in a patient: Who is refractory to initial therapy, Whose volume status and cardiac filling pressures are unclear, Who has clinically significant hypotension (typically systolic blood pressure <80 mm Hg) or worsening renal function during therapy, or In whom documentation of an adequate hemodynamic response to the inotropic agent is necessary when chronic outpatient infusion is being considered. (Strength of Evidence = C)	Invasive hemodynamic monitoring should be considered in a patient: • who is refractory to initial therapy, • whose volume status and cardiac filling pressures are unclear, • who has clinically significant hypotension (typically SBP < 80mm Hg) or worsening renal function during therapy, or • who is being considered for cardiac transplant and needs assessment of degree and reversibility of pulmonary hypertension, or • in whom documentation of an adequate hemodynamic response to the inotropic agent is necessary when chronic outpatient infusion is being considered. (Strength of Evidence = C)	Addition of cardiac transplant as criterion for invasive hemodynamic monitoring
12.23 (previous 12.21)	No changes		
12.24 (previous 12.22)	It is recommended that every effort be made to use the hospital stay for assessment and improvement of patient compliance via patient and family education and social support services (Section 8). (Strength of Evidence = C)	It is recommended that every effort be made to use the hospital stay for assessment and improvement of patient adherence via patient and family education and social support services (see Section 8). (Strength of Evidence = B)	Modification of strength of evidence from C to B; change in terminology (“compliance” to “adherence”)

(*continued on next page*)

Appendix A. (*continued*)

	2006 Guideline Recommendation	2010 Guideline Recommendation	Comments
12.25 (previous 12.23)	No changes		
12.26 (previous 12.24)	Discharge planning is recommended as part of the management of patients with ADHF. Discharge planning should address the following issues: • Details regarding medication, dietary sodium restriction, and recommended activity level • Follow-up by phone or clinic visit early after discharge to reassess volume status • Medication and dietary compliance • Monitoring of body weight, electrolytes, and renal function • Consideration of referral for formal disease management (Strength of Evidence = C)	Discharge planning is recommended as part of the management of patients with ADHF. Discharge planning should address the following issues: • Details regarding medication, dietary sodium restriction, and recommended activity level • Follow-up by phone or clinic visit early after discharge to reassess volume status • Medication and dietary compliance • Alcohol moderation and smoking cessation • Monitoring of body weight, electrolytes and renal function • Consideration of referral for formal disease management (Strength of Evidence = C)	Addition of alcohol moderation and smoking cessation
	Section 13: Evaluation and Therapy for Heart Failure in the Setting of Ischemic Heart Disease		
13.1	Assessment for risk factors for CAD is recommended in all patients with chronic HF regardless of EF. (Strength of Evidence = A) The diagnostic approach for CAD should be individualized based on patient preference and comorbidities, eligibility and willingness to perform revascularization. (Strength of Evidence = C)	Ongoing assessment for risk factors for CAD is recommended in all patients with chronic HF regardless of LVEF. (Strength of Evidence = A)	Moved diagnostic portion of recommendation to 13.2
13.2		It is recommended that the diagnostic approach for CAD be individualized based on patient preference and comorbidities, eligibility, symptoms suggestive of angina and willingness to undergo revascularization. (Strength of Evidence = C)	Previously part of 13.1
13.3 (previous 13.2)	It is recommended that patients with HF and angina undergo cardiac catheterization with coronary angiography to assess for potential revascularization. (Strength of Evidence = B)	It is recommended that patients with HF and symptoms suggestive of angina undergo cardiac catheterization with coronary angiography to assess for potential revascularization. (Strength of Evidence = B)	Modification of wording
13.4 (previous 13.3)	It is recommended that patients with HF, no angina, and known CAD should undergo noninvasive stress imaging and/or coronary angiography to assess severity of coronary disease and the presence of ischemia. (Strength of Evidence = C)	It is recommended that, at the initial diagnosis of HF and any time symptoms worsen without obvious cause, patients with HF, no angina, and known CAD should undergo risk assessment that may include noninvasive stress imaging and/or coronary angiography to assess severity of coronary disease and the presence of ischemia. (Strength of Evidence = C)	Clarification of type and timing of risk assessments
13.5 (previous 13.4)	No changes		
13.6 (previous 13.5)	No changes		

13.7 (previous 13.6)	Any of the following imaging tests may be used to identify inducible ischemia or viable but nocontractile myocardium: • Exercise or pharmacologic stress myocardial perfusion imaging • Exercise or pharmacologic stress echocardiography • Cardiac magnetic resonance imaging • Positron emission tomography scanning (Strength of Evidence = B)	Any of the following imaging tests should be considered to identify inducible ischemia or viable myocardium: • Exercise or pharmacologic stress myocardial perfusion imaging • Exercise or pharmacologic stress echocardiography • Cardiac magnetic resonance imaging • Positron emission tomography scanning (Strength of Evidence = B)	Modification of wording
13.8 (previous 13.7)	No changes		
13.9 (previous 13.8)	Antiplatelet therapy is recommended in patients with HF and CAD unless contraindicated. (Aspirin, Strength of Evidence = B; Clopidogrel, Strength of Evidence = C)	Antiplatelet therapy is recommended to reduce vascular events in patients with HF and CAD unless contraindicated. (aspirin, Strength of Evidence = A; clopidogrel, Strength of Evidence = B)	Addition of indication for antiplatelet therapy, and modification of strength of evidence
13.10 (previous 13.9)	ACE inhibitors are recommended in all patients with systolic dysfunction or preserved systolic function after an MI. (Strength of Evidence = A)	ACE inhibitors are recommended in all patients with either reduced or preserved LVEF after an MI. (Strength of Evidence = A)	Modification of terminology (“systolic dysfunction” changed to “reduced LVEF”)
13.11 (previous 13.10)	No changes		
13.12 (previous 13.11)	It is recommended that ACE-inhibitor and beta blocker therapy be initiated early (<48 hours) during hospitalization in hemodynamically stable post MI patients with LV dysfunction or HF. (Strength of Evidence = A)	It is recommended that ACE-inhibitor and beta blocker therapy be initiated early (<48 hours) during hospitalization in hemodynamically stable post-MI patients with reduced LVEF or HF. (Strength of Evidence = A)	Modification of terminology (“LV dysfunction” changed to “reduced LVEF”)
13.13 (previous 13.12)	No changes		
13.14 (previous 13.13)	Calcium channel blockers should be considered in patients with HF who have angina despite the optimal use of beta blockers and nitrates. Amlodipine and felodipine are the preferred calcium channel blockers in patients with angina and decreased systolic function. (Strength of Evidence = C)	Calcium channel blockers may be considered in patients with HF who have angina despite the optimal use of beta blockers and nitrates. Amlodipine and felodipine are the preferred calcium channel blockers in patients with angina and decreased systolic function. Based on available data, first generation calcium channel blockers (i.e. diltiazem, verapamil) should be avoided in patients with CAD, HF, and LVEF <40, unless necessary for heart rate control or other indications. (Strength of Evidence = C)	Addition of calcium channel blockers that should be avoided
13.15 (previous 13.14)	No changes		
13.16 (previous 13.15)	No changes		
	Section 14: Managing Patients with Hypertension and Heart Failure		
14.1	It is recommended that blood pressure be aggressively treated to lower systolic and usually diastolic levels. Target resting levels should be <130/<80 mm Hg, if tolerated. (Strength of Evidence = C)	It is recommended that blood pressure be optimally treated to lower systolic and usually diastolic levels. More than 1 drug may be required. Target resting levels should be <130/<80 mm Hg, if tolerated. (Strength of Evidence = A)	Modification of wording and change in strength of evidence from C to A

(*continued on next page*)

Appendix A. (*continued*)

	2006 Guideline Recommendation	2010 Guideline Recommendation	Comments
Previous 14.2			Deleted
14.2 (previous 14.3)	No changes		
14.3 (previous 14.4)	No changes		
14.4 (previous 14.5)	If BP remains >130/80 mm Hg then the addition of a diuretic is recommended, followed by a calcium antagonist or other antihypertensive drugs. (Strength of Evidence = C)	If blood pressure remains >130/80 mm Hg then the addition of a thiazide diuretic is recommended, followed by a dihydropyridine calcium antagonist (eg, amlodipine or felodipine) or other antihypertensive drugs. (Strength of Evidence = C)	Modified to specify thiazide diuretic or dihydropyridine calcium channel antagonist
14.5 (previous 14.6)	No changes		
14.6 (previous 14.7)	If blood pressure remains >130/80 mm Hg, a noncardiac-depressing calcium antagonist (eg, amlodipine) may be considered or other antihypertensive medication doses increased. (Strength of Evidence = C)	If blood pressure remains >130/80 mm Hg, a dihydropyridine calcium antagonist (eg, amlodipine or felodipine) may be considered or other antihypertensive medication doses increased. (Strength of Evidence = C)	Modified to specify dihydropyridine
	Section 15: Management of Heart Failure in Special Populations		
15.1	No changes		
15.2	No changes		
15.3	No changes		
15.4	No changes		
15.5	No changes		
15.6		ARBs are recommended for administration to symptomatic and asymptomatic women with an LVEF ≤ 40% who are intolerant to ACE inhibitors for reasons other than hyperkalemia or renal insufficiency. (Strength of Evidence = A)	New recommendation
15.7		The combination of hydralazine/isosorbide dinitrate is recommended as standard therapy for African American women with moderate to severe HF symptoms who are on background neurohormonal inhibition. (Strength of Evidence = B)	New recommendation
15.8 (previous 15.6)	No changes		

15.9 (previous 15.7)	No changes	
15.10 (previous 15.8)	No changes	
15.11 (previous 15.9)	No changes	
	Section 16: Myocarditis: Current Treatment	
16.1	No changes	
16.2	No changes	
	Section 17: Genetic Evaluation of Cardiomyopathy	New section

Appendix C. Financial Disclosure

Name	Consulting Fees/Honoraria	Speaker's Bureau	Research Grants	Equity Interests/ Stock/Stock Options	Equity Interests	Royalty Income	Non-Royalty Payments	Other Financial Benefit	Salary	Intellectual Property Rights	Fellowship Support
Nancy M. Albert, R.N., Ph.D	Medtronic										
Inder S. Anand, M.D., Ph.D.	Amgen Pharmaceuticals, Boston Scientific, Corventis, CVRx, Merck, Medtronic, N30, Paracor	Novartis Pharma-ceuticals	CVRx, Novartis Pharmaceuticals, Paracor						VA Medical Center		
J. Malcolm O. Arnold, M.D.	Abbott, Boehringer Ingelheim, GlaxoSmithKline, Merck-Frosst, Novartis, Pfizer										
John P. Boehmer, M.D.	Boston, Scientific, Medtronic, St. Jude		Boston Scientific, CardioMEMS, Medtronic, Novartis, Paracor								
John C. Burnett, M.D.	Anexon, Nile Therapeutics, Otsuka		Anexon, Bayer, BioRad, Merck, Nile Therapeutics, Trevena			Anexon, Nile Therapeutics					
John Chin, M.D.	Gilead, Otsuka	Boston Scientific, Eli Lilly, Gilead, Novartis									
Jay N. Cohn, M.D.			GlaxoSmithKline	CPC, LLC	HDT, Inc.	MLHFQ, NitroMed					
Sean P. Collins, M.D., MSc	Abbott Point-of-Care, Astellas, Bayer, Corthera, The Medicines Company, Otsuka		Abbott Point-of-Care, BRAHMS Diagnostics, National Institutes of Health/NHLBI								
Justin A. Ezekowitz, MBBCh	Amgen, Bristol-Myers Squibb, Pfizer		Amgen, Bristol-Myers Squibb, Merck, Ortho-Biotech/Johnson & Johnson								
Thomas Force, M.D.		Merck Schering Plough/Merck						GlaxoSmithKline			
Bart Galle, Ph.D.	disclosures: none										

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Sarah J. Goodlin, M.D.	Servier		Boston Scientific CARE, St. Jude Medical Foundation								
Barry H. Greenberg, M.D.	Biogen Idec, CardioMEMS, Corthera, Cytokinetics, GlaxoSmithKline, Otsuka, Paracor, St. Jude, Zensun	Gilead, Merck, Novartis, sanofi-aventis									
Ray E. Hershberger, M.D.	disclosures: none										
Steven R. Houser, Ph.D.	disclosures: none										
Jonathan G. Howlett, M.D.	AstraZeneca, Merck, Novartis, Schering, Servier	AstraZeneca, Merck, Novartis, Schering, Servier	AstraZeneca, Medtronic, Merck, Novartis, Schering, Servier								
Sharon A. Hunt, M.D.	disclosures: none										
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Stuart D. Katz, M.D.	Amgen, Dura Heart Terumo, Merck, Paracor										
Marc Klapholz, M.D.	GlaxoSmithKline, Medtronic, Paracor, St. Jude, Schering	GlaxoSmithKline									
Marvin W. Kronenberg, M.D.				Cardiovascular Services of America							
JoAnn Lindenfeld, M.D.	Astellas, Boston Scientific, Forest, Medtronic, N30		Merck								
Douglas L. Mann, M.D.	ARMGO Pharmaceuticals, Medtronic, Miragen, Nile Therapeutics, PeriCor Therapeutics				Miragen						

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Appendix C. (*continued*)

Name	Consulting Fees/Honoraria	Speaker's Bureau	Research Grants	Equity Interests/ Stock/Stock Options	Equity Interests	Royalty Income	Non-Royalty Payments	Other Financial Benefit	Salary	Intellectual Property Rights	Fellowship Support
Barry M. Massie, M.D.	ARCA, Boehringer, Bristol-Myers Squibb, Corthera, Cytokinetics, Duke Clinical Research Institute, Merck, Nile Therapeutics, Novartis, sanofi-aventis, St. Jude, Takeda, Trevena	Merck									
Mandeep R. Mehra, M.D.	Geron, Johnson & Johnson, Medtronic, Pericor, Solvay, St. Jude		National Institutes of Health								
Luisa Mestroni, M.D.		M01 RR00051-1575						University of Colorado (employee)			
Alan B. Miller, M.D.	disclosures: none										
Debra K. Moser, R.N., DNSc.	disclosures: none										
Mariann R. Piano, R.N., Ph.D.	disclosures: none										
Richard J. Rodeheffer, M.D.	disclosures: none										
Joseph G. Rogers, M.D.	Forrest Pharmaceuticals, Thoratec	Boston Scientific, Medtronic									
Christine E. Seidman, M.D.			HHMI & NIH								
Randall C. Starling, M.D., MPH	BioControl, Medtronic, Novartis		Biotronik, Medtronic, Novartis, Thoratec	CardioMEMS							Medtronic
William G. Stevenson, M.D.	disclosures: none										

Wendy Gattis Stough, Pharm.D.	ARCA Discovery, Inc., Gilead Sciences, Inc., GlaxoSmithKlline, Heart Failure Society of America, Medtronic, Otsuka, Scios										
W.H. Wilson Tang, M.D.	Medtronic, Merck & Company		Abbott Laboratories								
Matthew R.G. Taylor, M.D., Ph.D.		Genzyme Therapeutics	Muscular Dystrophy Association/March of Dimes/Genzyme Therapeutics								
John R. Teerlink, M.D.	Abbott Laboratories, BAS Medical/ Corthera, Biogen Idec, Bristol-Myers Squibb, CardioDynamics, CardioMEMS, CoGeneSys, Cytokinetics, Geron, GlaxoSmithKline, Icon Medical Imaging, Indigo Pharma, Kowa Pharma, Luitpold Pharma, Merck, Momentum Research, Nile Therapeutics, Novartis, sanofi-aventis, Scios/ Johnson & Johnson		Abbott Laboratories, BAS Medical/Corthera, Bristol-Myers Squibb, Cytokinetics, GlaxoSmithKline, Merck, National Institutes of Health, Novartis, sanofi-aventis	Cytokinetics							
Jeffery A. Towbin, M.D.	disclosure: none										
Mary N. Walsh, M.D.	ARCA, Boston Scientific, EMERGE, Medtronic, United Health Care										
Clyde W. Yancy, M.D.	disclosures: none										
Cheryl Yano	disclosures: none										
Michael R. Zile, M.D.	ABIM, BMS, CorAssist, CVRx, DC Devices, Gilead, Medtronic, Merck, N30, Novartis, OCD/J&J, sanofi-aventis, Up-To-Date		BMS, Boston, Scientific, CVRx, Department of VA, Gilead, Medtronic, Merck, National Heart, Lung and Blood Institute, Novartis, OCD/J&J, Pfizer, sanofi-aventis						Department of VA, MUSC, National Heart, Lung and Blood Institute	MUSC, OCD/ J&J	

Section 2: Conceptualization and Working Definition of Heart Failure

Heart failure (HF) remains a major and growing societal problem despite advances in detection and therapy.[1-4] However, there is no widely accepted characterization and definition of HF, probably because of the complexity of the syndrome. The conceptualization and working definition of HF presented here emerged as these guidelines were developed. They are critical to understanding HF and approaching its treatment appropriately.

Conceptual Background. HF is a syndrome rather than a primary diagnosis. It has many potential etiologies, diverse clinical features, and numerous clinical subsets. Patients may have a variety of primary cardiovascular diseases and never develop cardiac dysfunction, and those in whom cardiac dysfunction is identified through testing may never develop clinical HF. In addition to cardiac dysfunction, other factors, such as vascular stiffness, dyssynchrony, and renal sodium handling, play major roles in the manifestation of the syndrome of HF.

Patients at risk for many cardiovascular diseases are at risk for HF. Early identification and treatment of risk factors is perhaps the most significant step in limiting the public health impact of HF.[5-7] Emphasis on primary and secondary prevention is particularly critical because of the difficulty of successfully treating left ventricular (LV) dysfunction, especially when severe.[5] Current therapeutic advances in the treatment of HF do not make prevention any less important.

Although HF is progressive, current therapy may provide stability and even reversibility. The inexorable progression of HF from LV remodeling and dysfunction is no longer inevitable. Prolonged survival with mild to moderate LV dysfunction is now possible. Therapy with angiotensin-converting enzyme inhibitors (or angiotensin receptor blockers), beta blockers, and cardiac resynchronization therapy can lead to slowing or to partial reversal of remodeling.

Because of this prolonged survival, comorbid conditions, such as coronary artery disease or renal failure, can progress, complicating treatment. Given this prolonged survival, considerable attention is devoted in this guideline to disease management, the use of multidrug therapy, and the management of patients with HF at the end of life.

Working Definition. Although HF may be caused by a variety of disorders, including valvular abnormalities and dysrhythmias, the following comprehensive guideline and this working definition focus on HF primarily from the loss or dysfunction of myocardial muscle or interstitium.

Table 2.1. Additional HF Definitions

"HF With Reduced Left Ventricular Ejection Fraction (LVEF)" Sometimes: "HF With a Dilated Left Ventricle"	A clinical syndrome characterized by signs and symptoms of HF and reduced LVEF. Most commonly associated with LV chamber dilation.
"HF With Preserved LVEF" Sometimes: "HF With Nondilated LV"	A clinical syndrome characterized by signs and symptoms of HF with preserved LVEF. Most commonly associated with a nondilated LV chamber. May be the result of valvular disease or other causes (Section 11).
"Myocardial Remodeling"	Pathologic myocardial hypertrophy or dilation in response to increased myocardial stress. These changes are generally accompanied by pathologic changes in the cardiac interstitium. Myocardial remodeling is generally a progressive disorder.

HF is a syndrome caused by cardiac dysfunction, generally resulting from myocardial muscle dysfunction or loss and characterized by either LV dilation or hypertrophy or both. Whether the dysfunction is primarily systolic or diastolic or mixed, it leads to neurohormonal and circulatory abnormalities, usually resulting in characteristic symptoms such as fluid retention, shortness of breath, and fatigue, especially on exertion. In the absence of appropriate therapeutic intervention, HF is usually progressive at the level of both cardiac function and clinical symptoms. The severity of clinical symptoms may vary substantially during the course of the disease process and may not correlate with changes in underlying cardiac function. Although HF is progressive and often fatal, patients can be stabilized and myocardial dysfunction and remodeling may improve, either spontaneously or as a consequence of therapy. In physiologic terms, HF is a syndrome characterized by either or both pulmonary and systemic venous congestion and/or inadequate peripheral oxygen delivery, at rest or during stress, caused by cardiac dysfunction.

Additional Definitions

HF is often classified as HF with reduced systolic function versus HF with preserved systolic function. Myocardial remodeling often precedes the clinical syndrome of HF. Additional definitions are provided in Table 2.1. A table of acronyms and their meaning is provided in Appendix B.

Disclosures

See Appendix C.

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Appendix B. Acronyms

Acronym	Meaning
ACE	angiotensin converting enzyme
ADA	American Diabetes Association
ADHF	acute decompensated heart failure
AF	atrial fibrillation
AHA/ACC	American Heart Association/American College of Cardiology
ALVD	asymptomatic left ventricular dysfunction
ARB	angiotensin receptor blocker
ARVD/C	arrhythmogenic right ventricular dysplasia/ cardiomyopathy
AV	arteriovenous
BMI	body mass index
BNP	B-type natriuretic peptide
BUN	blood urea nitrogen
CABG	coronary artery bypass graft
CAD	coronary artery disease
CHD	congenital heart disease
CI	confidence interval
CK-MM	creatinine kinase MM isoenzyme
COPD	chronic obstructive pulmonary disease
COX-2	cyclooxygenase-2
CPAP	continuous positive airway pressure
CPR	cardiopulmonary resuscitation
CR/XL	controlled release/extended release
CREST	a limited cutaneous form of scleroderma defined by calsinosis, Raynaud's syndrome, esophageal dysmotility, sclerodactyly, and telangiectasia
CRT	cardiac resynchronization therapy
CRT-D	cardiac resynchronization therapy device and defibrillator
CTR	cardiothoracic ratio
DASH	Dietary Approaches to Stop Hypertension
DBP	diastolic blood pressure
DCM	dilated cardiomyopathy
DNR	do not resuscitate
DVT	deep venous thrombosis
ECG	electrocardiogram
ED	emergency department
EP, EPS	electrophysiology, electrophysiology study
EVCPP	endoventricular circular patch plasty
FDC	familial dilated cardiomyopathy
GFR, eGFR	glomerular filtration rate, estimated glomerular filtration rate
HCM	hypertrophic cardiomyopathy
HF	heart failure
HFSA	Heart Failure Society of America
HR	hazard ratio
ICD	implantable cardioverter defibrillator
INR	international normalized ratio
JVP	jugular venous pressure
LA	left atrial
LMWH	low molecular weight heparin
LV	left ventricular
LVAD	left ventricular assist device
LVEF	left ventricular ejection fraction
LVH	left ventricular hypertrophy
LVNC	left ventricular noncompaction
MI	myocardial infarction
MRI	magnetic resonance imaging
NCEP	National Cholesterol Education Program
NIV	non-invasive ventilation
NSAID	non-steroidal anti-inflammatory drug
NT-proBNP	N-terminal pro-B-type natriuretic peptide
NYHA	New York Heart Association
OMIM	Online Mendelian Inheritance in Man (online resource)
OU	observation unit
PCI	percutaneous coronary intervention
PCWP	pulmonary capillary wedge pressure
PE	pulmonary embolism
PET-CT	positron emission tomography − computed tomography
PMI	point of maximal impulse
PND	paroxysmal nocturnal dyspnea
PPAR-α	peroxisome proliferator-activated receptor-alpha
PUFA	polyunsaturated fatty acids
PVC	premature ventricular contraction
QTc	QT interval corrected for heart rate
RAAS	renin-angiotensin-aldosterone system
RCM	restrictive cardiomyopathy
RV	right ventricular
SAECG	signal-averaged electrocardiogram
SAVER	surgical anterior ventricular endocardial restoration
SBP	systolic blood pressure
SCD	sudden cardiac death
SDC	serum digoxin concentration
SPECT	single-photon emission computed tomography
SSRI	selective serotonin reuptake inhibitors
STEMI	ST-elevation myocardial infarction
TNF-α	tumor necrosis factor-alpha
UFH	unfractionated heparin
USDA	United States Department of Agriculture
VE/VCO_2	ventilation equivalent of carbon dioxide (production slope)
VF	ventricular fibrillation
VT	ventricular tachycardia
Clinical Trials	
Acronym	**Full Trial Name**
ACCOMPLISH	Avoiding Cardiovascular Events Through Combination Therapy in Patients Living with Systolic Hypertension
ADHERE	Acute Decompensated Heart Failure National Registry (Registry)
AFFIRM	Atrial Fibrillation Follow-Up Investigation of Rhythm Management
A-HeFT	African-American Heart Failure Trial
ALLHAT	Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial
ALOFT	Aliskiren Observation of Heart Failure Treatment
B-CONVINCED	Beta Blocker Continuation Versus Interruption on Patients with Congestive Heart Failure Hospitalized for a Decompensation Episode
CANPAP	Canadian Continuous Positive Airway Pressure for Patients with Central Sleep Apnea and Heart Failure
CAPRICORN	Carvedilol Post-Infarct Survival Control in Left Ventricular Dysfunction
CARE-HF	Cardiac Resynchronization-Heart Failure
CHARM	Candesartan in Heart Failure Assessment of Reduction in Mortality and Morbidity (Also CHARM-Added, CHARM-Alternative, CHARM-Preserved)
CIBIS	Cardiac Insufficiency Bisoprolol Study
COACH	Coordinating Study Evaluating Outcomes of Advising and Counseling in Heart Failure
COMET	Carvedilol or Metoprolol European Trial
COMPANION	Comparison of Medical Therapy, Pacing, and Defibrillation in Chronic Heart Failure
CONSENSUS II	Cooperative New Scandinavian Enalapril Survival Study II
COPERNICUS	Carvedilol Prospective Randomized Cumulative Survival Study
DIG	Digitalis Investigation Group
EFFECT	Enhanced Feedback for Effective Cardiac Treatment (Evaluation Tool)
EPHESUS	Epleronone Post-Acute Myocardial Infarction Heart Failure Efficacy and Survival Study
ESCAPE	Evaluation Study of Congestive Heart Failure and Pulmonary Artery Catheterization Effectiveness
EUROPA	European Trial on Reduction of Cardiac Events with Perindopril in Stable Coronary Artery Disease
FAIR-HF	Ferinject Assessment in Patients with Iron Deficiency and Chronic Heart Failure
GISSI	Gruppo Italiano Per Lo Studio Della Sopravvivenza Nell'infarto Miocardico (GISSI-Prevenzione, GISSI-HF)
GUSTO-1	Global Utilization of Streptokinase and Tissue Plasminogen Activator for Occluded Coronary Arteries

(*continued*)

(*continued on next page*)

Appendix B. (*continued*)

HEART	Heart Failure Revascularization Trial
HELP	Hospitalized Elderly Longitudinal Project
HERS	Heart and Estrogen/Progestin Replacement Study
HF-ACTION	A Controlled Trial Investigating Outcomes of Exercise Training
HOBIPACE	Homburg Biventricular Pacing Evaluation
HOPE	Heart Outcomes Prevention Evaluation
HOT	Hypertension Optimal Treatment
INTERMACS	Interagency Registry for Mechanically Assisted Circulatory Support (Registry)
I-PRESERVE	Irbesartan in Heart Failure with Preserved Ejection Fraction
IRON-HF	Iron Supplementation in Heart Failure Patients with Anemia
ISIS-4	Fourth International Study of Infarct Survival
MADIT-CRT	Multi-Center Automatic Defibrillator Implantation Trial with Cardiac Resynchronization Therapy
MERIT-HF	Metoprolol CR?XL Randomized Intervention Trial in Congestive Heart Failure
MIRACLE	Multicenter Insync Clinical Study
MTT	Myocarditis Treatment Trial
MUSTT	Multicenter Unsustained Tachycardia Trial
NHANES	National Health and Nutrition Examination Survey Epidemiologic Follow-Up Study
OAT	Occluded Artery Trial
OPTIMAAL	Optimal Trial in Myocardial Infarction with the Angiotensin II Antagonist Losartan
OPTIME-HF	Outcomes of a Prospective Trial of Intravenous Milrinone for Exacerbations of Chronic Heart Failure
OPTIMIZE-HF	Organized Program to Initiate Lifesaving Treatment in Hospitalized Patients with Heart Failure (Registry)
PRIDE	N-Terminal Pro-BNP Investigation of Dyspnea in the Emergency Department
PRIMA	Can Pro-Brain-Natriuretic-Peptide Guided Therapy of Chronic Heart Failure Improve Heart Failure Morbidity and Mortality?
PROVED	Prospective Randomized Study of Ventricular Function and Efficacy of Digoxin
RADIANCE	Randomized Assessment of Digoxin on Inhibitors of the Angiotensin Converting System
RALES	Randomized Aldactone Evaluation Study
RED-HF	Reduction of Events with Darbepoetin Alfa in Heart Failure
REMATCH	Randomized Evaluation of Mechanical Assistance for the Treatment of Congestive Heart Failure
REVERSE	Resynchronization Reverses Remodeling in Systolic Left Ventricular Dysfunction
REVERT	Reversal of Ventricular Remodeling with Toprol-XL
SCD-HeFT	Sudden Cardiac Death in Heart Failure Trial
SENIORS	Study of the Effects of Nebivolol Intervention on Outcomes and Rehospitalization in Seniors with Heart Failure
SOLVD	Studies of Left Ventricular Dysfunction
STARS-BNP	Systolic Heart Failure Treatment Supported By BNP
STICH	Surgical Treatment for Ischemic Heart Failure
SUPPORT	Study to Understand Prognoses and Preferences for Outcomes and Risks of Treatment
TIME-CHF	Trial of Intensified Vs Standard Medical Therapy in Elderly Patients with Congestive Heart Failure
UKPDS	United Kingdom Prospective Diabetes Study
Val-HeFT	Valsartan Heart Failure Trial
VALIANT	The Valsartan in Acute Myocardial Infarction Trial
V-HeFT	Vasodilator Heart Failure Trial
VMAC	Vasodilator in the Management of Acute Heart Failure
WASH	Warfarin/Aspirin Study in Heart Failure
WATCH	Warfarin and Antiplatelet Therapy in Chronic Heart Failure

Section 3: Prevention of Ventricular Remodeling, Cardiac Dysfunction, and Heart Failure

Overview

Heart failure (HF) is an all-too-frequent outcome of hypertension and arterial vascular disease, making it a major public health concern.[1,2] Epidemiologic, clinical, and basic research have identified a number of antecedent conditions that predispose individuals to HF and its predecessors, left ventricular (LV) remodeling and dysfunction.[3–11] Recognition that many of these risk factors can be modified and that treating HF is difficult and costly has focused attention on preventive strategies for HF.

Development of both systolic and diastolic dysfunction related to adverse ventricular remodeling may take years to produce significant ill effects.[12–18] Although the precise mechanisms for the transition to symptomatic HF are not clear, many modifiable factors have been identified that predispose or aggravate the remodeling process and the development of cardiac dysfunction. Treatment of systemic hypertension, with or without LV hypertrophy, reduces the development of HF.[19–27] Prevention of myocardial infarction (MI) in patients with atherosclerotic cardiovascular disease is a critical intervention, since occurrence of MI confers an 8- to 10-fold increased risk for subsequent HF.[20] Other modifiable risk factors include anemia, diabetes, hyperlipidemia, obesity, valvular abnormalities, alcohol, certain illicit drugs, some cardiotoxic medications, and diet.[28,29] Consumption of one or more breakfast cereals per week and four or more servings of fruits and vegetables per day, as well as frequent exercise and moderate alcohol use have been individually and jointly associated with lower lifetime risk of HF in men.[29]

Patients with Risk Factors for Ventricular Remodeling, Cardiac Dysfunction, and HF

Recommendations

3.1 A careful and thorough clinical assessment, with appropriate investigation for known or potential risk factors, is recommended in an effort to prevent development of LV remodeling, cardiac dysfunction, and HF. These risk factors include, but are not limited to, hypertension, hyperlipidemia, atherosclerosis, diabetes mellitus, valvular disease, obesity, physical inactivity, excessive alcohol intake, dietary choices, and smoking. (Strength of Evidence = A)

3.2 The recommended goals for the management of specific risk factors for the development of cardiac dysfunction and HF are shown in Table 3.1.

These recommendations are based are well-documented data.[17,20,30–39]

Background

Hypertension. It is estimated that 74% of patients with HF have a history of blood pressure >140/90 mmHg.[40] A history of hypertension has been associated with a higher risk of HF hospitalization among post-MI patients without a prior HF history enrolled in the EPHESUS study.[41] Hypertension is a particularly significant risk factor for the development of HF in women.[9] Results from numerous randomized controlled clinical trials have proven antihypertensive therapy can reduce the incidence of symptomatic HF by 50% to 80%. The risk reduction (both absolute and relative) is greatest in severe hypertension (>160/110 mm Hg) and least in those with mild hypertension (>145/95 mm Hg). Optimal blood pressure for the prevention of HF is not known. Data from recent trials suggest that 130/80 mm Hg or lower is the optimal blood pressure for patients with documented end-organ disease (diabetes with nephropathy, patients with proteinuria).[31] The World Health Organization has suggested an optimal blood pressure of 115/75 mm Hg for individuals with no documented end-organ disease. It is uncertain whether additional therapy to lower blood pressure further will confer additional benefit.

Reducing blood pressure is a critical component of HF prevention. The choice of antihypertensive agent should be made in the context of the patient's cardiovascular risks and comorbidities or other compelling indications.[31] In general, angiotensin converting enzyme (ACE) inhibitors, angiotensin receptor blockers (ARBs), beta blockers, and diuretics when used as anti-hypertensives all decrease the risk of developing HF, while amlodipine is associated with increased risk.[42–50] However, in the Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT), amlodipine was associated with a lower overall risk of cardiovascular events as compared to lisinopril or chlorthalidone.[48–50] Meta- analyses have confirmed these findings.[51,52] In the Avoiding Cardiovascular Events through Combination Therapy in Patients Living with Systolic Hypertension (ACCOMPLISH) trial, a combination of benazepril and amlodipine decreased time to cardiovascular death or cardiovascular events by 20% compared to the combination of benazepril-hydrochlorthiazide without an increase in HF hospitalizations.[53]

Restriction of dietary sodium intake has been associated with blood pressure reduction similar to single drug therapy. The Dietary Approaches to Stop Hypertension (ie, DASH) diet, rich in potassium and calcium, has been associated with a reduced incidence of hypertension requiring drug therapy.[54] Lower rates of HF have been observed

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Table 3.1. Goals for the Management of Risk Factors for the Development of Heart Failure

Risk Factor	Population	Treatment Goal	Strength of Evidence
Hypertension	No diabetes or renal disease	<140/90 mmHg	A
	Diabetes	<130/80 mmHg	A
	Renal insufficiency and >1g/day of proteinuria	127/75	A
	Renal insufficiency and ≤1 g/day of proteinuria	130/85	A
	Everyone with hypertension	Limit sodium to ≤1500 mg/day	A
Diabetes	See American Diabetes Association (ADA) Guideline		
Hyperlipidemia	See National Cholesterol Education Program (NCEP) Guideline		
Physical Inactivity	Everyone	Sustained aerobic activity 20-30 minutes, 3-5 times weekly	B
Obesity	BMI >30	Weight reduction to achieve BMI <30	C
Excessive alcohol intake	Men	Limit alcohol intake to 1-2 drink equivalents per day	C
	Women	1 drink equivalent per day	
	Those with propensity to abuse alcohol or with alcoholic cardiomyopathy	Abstention	
Smoking	Everyone	Cessation	A
Vitamin/mineral deficiency	Everyone	Diet high in K^+/calcium	B
Poor diet	Everyone	4 or more servings of fruit and vegetables per day; One or more servings of breakfast cereal per week	B

in both men and women consuming diets consistent with DASH.[55] See Table 3.2 for sodium equivalents.

Hyperlipidemia. In a large randomized study of a statin versus placebo in patients with MI and elevated low-density lipoprotein, treatment with a statin was associated with a highly significant reduction in all-cause mortality and recurrent MI.[8,37] A 20% reduction in the incidence of HF was noted in patients treated with statin therapy. Recurrent MI during this study was associated with a large relative increase in mortality and HF; thus, it is possible that the reduction in the risk of incident HF may have been related to the reduction in recurrent MI rather than to a direct effect of the statin.

Similarly, in the Heart Protection Study, randomization to simvastatin was associated with a 14% reduction in the risk of hospitalization or death due to HF.[56] Whether the reduction was due to a direct effect on HF or an indirect effect through a reduction in vascular events could not be determined from the analysis. In large randomized, controlled trials, statins have not been shown to improve clinical outcome among patients with existing New York Heart Association (NYHA) class II-IV HF.[57,58]

Although dyslipidemia is clearly associated with the development of coronary heart disease, its contribution to incident HF is less clear. Data from the Physicians' Health Study did not find an association between high total cholesterol or low HDL cholesterol and incident HF after adjustment for traditional cardiovascular risk factors.[59] There is no indication to use statins specifically for the treatment of HF, but statins are indicated to treat hyperlipidemia in HF patients.

Table 3.2. Sodium Equivalents

Salt	Sodium Chloride	Sodium
¼ teaspoon	1550 mg	600 mg
½ teaspoon	3100 mg	1200 mg
¾ teaspoon	4650 mg	1800 mg
1 teaspoon	6100 mg	2400 mg

Obesity. The American Heart Association and the European Society of Cardiology recommend an ideal body mass index (BMI) of 25−27 kg/m^2. BMI is calculated by dividing the patient's weight in kilograms by his or her height in meters squared. Obesity is defined as a BMI ≥30, overweight as a BMI ≥25. Waist-to-hip ratio may be a more powerful predictor than BMI of the risk of MI and subsequent HF.[60] Adults with BMI of 25 or 30 kg/m^2 who had a higher waist circumference had higher rates of HF incidence than those with lower waist circumference.[61] Obesity is associated with metabolic syndrome, increasingly accepted as a major risk factor for the development of cardiovascular disease. Excessive body fat results in increased metabolic demand, ventricular hypertrophy, and sleep-disordered breathing, all of which promote the development of HF. The relationship between obesity and the risk of HF is well established,[7] although some data suggest that other pathophysiologic processes associated with obesity such as inflammation may have a greater influence on the development of HF than obesity itself.[62] There is an increasing body of opinion that obesity is associated with a distinct form of cardiomyopathy. A retrospective analysis of echocardiograms for 13,382 subjects with BMI data revealed no association between LV systolic function and BMI, suggesting that other mechanisms may play a role in the development of HF in obese

persons.[63] However, in a study of 2,042 adults in Olmsted County, Minnesota, LV diastolic dysfunction was strongly associated with waist-to-hip ratio, even after adjustment for standard cardiovascular risk factors.[64]

Weight reduction has been shown to improve most of the adverse effects of obesity. It is likely that weight reduction in obese individuals reduces the likelihood of subsequent HF, although no data exist to confirm this hypothesis.

Physical Inactivity. The benefits of exercise are well documented and include reduction of recurrent MI in survivors of MI, improved exercise capacity, improved affect and quality of life, and better control of hypertension. These results are achieved with a minimum of 20−30 minutes of sustained submaximal exercise 3−5 times per week (see Section 6).[65] In one population-based study of men, exercising 5 or more times per week reduced the lifetime risk of HF at age 40 years.[29]

Alcohol Intake. Alcoholic cardiomyopathy is associated with a substantial intake of alcohol (70 g or greater per day of chronic ingestion). Avoiding substantial ingestion of alcohol is clearly advisable, but the safe level of moderate ingestion has been difficult to define. Other factors such as drinking patterns, beverage type, and genetic variations affecting alcohol metabolism may also influence the relationship between alcohol and incident HF.[66] There are conflicting reports regarding the effects of alcohol ingestion upon left ventricular ejection fraction (LVEF) in those with and without HF. At present, 2 drinks per day for men and 1 drink per day for women is considered acceptable, even in individuals with other cardiovascular risk factors. One drink is equivalent to 12−14 g of alcohol, the amount in 1.5 ounces of 80 proof spirits, 12 ounces of beer, or 5 ounces of wine. Those with for a propensity to abuse alcohol should be counseled to abstain. Population-based studies have established an association between moderate alcohol intake (up to 2 drinks per day for men or 1 drink per day for women) and a reduction in incident HF.[29,67,68] One study also suggests that light to moderate alcohol consumption is not associated with an adverse prognosis in patients with LV systolic dysfunction.[68] While some data suggest that low risk drinking decreases the risk of HF in patients with antecedent coronary artery disease, it seems prudent to follow the national recommendations referred to above.

Smoking Cessation. There is a substantial body of data concerning the adverse effects of smoking in patients with vascular disease or reduced LVEF. Smoking cessation is associated with a 50% reduction in 5-year mortality in survivors of acute MI.[69] In the Studies of Left Ventricular Dysfunction (SOLVD) study of patients with either symptomatic or asymptomatic LV dysfunction, nonsmokers or former smokers showed improved mortality when compared with current smokers.[70,71] These and other observational data suggest smoking cessation dramatically reduces adverse outcomes in patients with established vascular disease and those with established ventricular remodeling or dysfunction.

Diabetes. Diabetes is a known predictor of HF in patients with and without established cardiovascular disease.[72−75] Women with diabetes are at particular risk. In the Heart and Estrogen/Progestin Replacement Study (HERS), postmenopausal women with diabetes had a 3.0% annual incidence of developing HF even in the absence of other risk factors.[72] Leung et al reported the adjusted rate of incident HF among patients with type-2 diabetes as 794 cases per 100,000 person years, compared with 275 per 100,000 person-years in the general population, even after adjustment for demographic differences.[76] In the diabetic heart, myocyte free fatty acid uptake and oxidation is increased. This leads to free fatty acid induced insulin resistance and intracellular accumulation of triglyceride and free fatty acids, which may contribute to the development of cardiomyopathy. Downregulation of PPAR-α also appears to play an important role.[77] Additionally, many patients with diabetes have other comorbidities that are also associated with the development of HF, including ischemic heart disease, hypertension, and LV hypertrophy.[77] More research is needed to evaluate the effect of glycemic control on HF risk. In the United Kingdom Prospective Diabetes Study (UKPDS), the absolute risk of a HF event was significantly lower for patients randomized to tight glycemic control as compared to less tight control (RR 0.44, 99% CI 0.2−0.94, P=.0043).[78]

Recommendation

3.3 ACE inhibitors are recommended for prevention of HF in patients at high risk of this syndrome, including those with coronary artery disease, peripheral vascular disease, or stroke. Patients with diabetes and another major risk factor or patients with diabetes who smoke or have microalbuminuria are also at high risk and should receive ACE inhibitors. (Strength of Evidence = A)

Background

Findings from at least three randomized, controlled trials support the use of ACE inhibitors in patients at high risk for the development of HF. In one study of patients older than age 55 with documented vascular disease or multiple cardiac risk factors, including diabetes, treatment with an ACE inhibitor reduced the annual risk of developing HF by 23%.[20] A study of patients older than age 18 with documented coronary artery disease showed that treatment with an ACE inhibitor reduced total mortality by 14% over 4.2 years, even though patients were already receiving aggressive treatment for vascular disease.[44] In a third study, patients with previous stroke and mild hypertension treated with an ACE inhibitor-based antihypertensive regimen showed a 26% reduction in subsequent HF.[33]

Several trials studied the use of an ARB in patients at high risk for developing HF.[79,80] In one the composite cardiovascular event rate did not differ in patients with diabetes treated with an ARB, amlodipine, or placebo.[79] In another, patients at risk for or with cardiovascular disease, including HF, did better when treated with an ARB on top of conventional antihypertensive therapy as compared supplementary conventional treatment.[80] A recent trial comparing the use of an ACE inhibitor versus an ARB in a population with vascular disease or high-risk diabetes, but no HF, found that the ARB was non-inferior to the ACE inhibitor in preventing the primary end point of cardiovascular death, MI, stroke, or HF hospitalization.[81] Based on these results, it is reasonable to say that, at least in those high risk patients who do not tolerate an ACE inhibitor, an ARB should be used.

Recommendation

3.4 Beta blockers are recommended for patients with prior MI to reduce mortality, recurrent MI, and the development of HF. (Strength of Evidence = A)

Background

Beta blockers are known to reduce cardiac ischemia, reinfarction, and myocardial remodeling after acute MI. Studies in patients with recent MI (most published in the prethrombolytic era) have shown that beta blockers are associated with a large reduction in HF and recurrent all-cause hospitalizations, HF hospitalizations, and recurrent MI.[46,82–90] More recent data confirm this finding, showing risk reduction for the development of HF in the 25% to 45% range 1 year after MI.[91] Data from the Carvedilol Post-Infarct Survival Control in Left Ventricular Dysfunction (CAPRICORN) Echo Substudy demonstrated a significant decrease in LV end systolic volume and a significant increase in LVEF at 6 months post-MI for patients randomized to carvedilol as compared to placebo.[92] Patients most at risk for HF and death after MI - women and patients with advanced age, diabetes, renal disease, or previous revascularization - appear to derive the most benefit, but unfortunately are less likely to receive beta blockade post MI.[93,94] Even among patients with asymptomatic LV dysfunction without a recent MI, beta blocker therapy has been shown to decrease LV end systolic and end diastolic volume and increase LVEF at 6 and 12 months as compared to placebo.[95]

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Section 4: Evaluation of Patients for Ventricular Dysfunction and Heart Failure

Overview

Patients undergoing evaluation for ventricular dysfunction and heart failure (HF) fall into 3 general groups: (1) patients at risk of developing HF, (2) patients suspected of having HF based on signs and symptoms or incidental evidence of abnormal cardiac structure or function, and (3) patients with established symptomatic HF.

Patients at Risk for HF. Patients identified to be at risk for HF require aggressive management of modifiable risk factors as outlined in Section 3 of this guideline. Patients with risk factors may have undetected abnormalities of cardiac structure or function. In addition to risk factor reduction, these patients require careful assessment for the presence of symptoms of HF and, depending on their underlying risk, may warrant noninvasive evaluation of cardiac structure and function.

Patients Suspected of Having HF. The evaluation of patients suspected of having HF focuses on interpretation of signs and symptoms that have led to the consideration of this diagnosis. Careful history and physical examination, combined with evaluation of cardiac structure and function, should be undertaken to determine the cause of symptoms and to evaluate the degree of underlying cardiac pathology.

Patients With Established HF. The evaluation of patients with an established diagnosis of HF is undertaken to identify the etiology, assess symptom nature and severity, determine functional impairment, and establish a prognosis. Follow-up of patients with HF or cardiac dysfunction involves continuing reassessment of symptoms, functional capacity, prognosis, and therapeutic effectiveness.

Evaluation of Patients at Risk

Recommendations

4.1 Evaluation for clinical manifestations of HF with a routine history and physical examination is recommended in patients with the medical conditions or test findings listed in Table 4.1. (Strength of Evidence = B)

4.2 Assessment of Cardiac Structure and Function. Echocardiography with Doppler is recommended to determine cardiac structure and function in asymptomatic patients with the disorders or findings listed in Table 4.2. (Strength of Evidence = B)

Table 4.1. Indications for Evaluation of Clinical Manifestations of HF

Conditions	Hypertension
	Diabetes
	Obesity
	CAD (eg, after MI, revascularization)
	Peripheral arterial disease or cerebrovascular disease
	Valvular heart disease
	Family history of cardiomyopathy in a first-degree relative
	History of exposure to cardiac toxins
	Sleep-disordered breathing
Test Findings	Sustained arrhythmias
	Abnormal ECG (eg, LVH, left bundle branch block, pathologic Q waves)
	Cardiomegaly on chest X-ray

Table 4.2. Assess Cardiac Structure and Function in Patients with the Following Disorders or Findings

Coronary artery disease (eg, after MI, revascularization)
Valvular heart disease
Family history of cardiomyopathy in a first-degree relative
Atrial fibrillation or flutter
Electrocardiographic evidence of LVH, left bundle branch block, or pathologic Q waves
Complex ventricular arrhythmia
Cardiomegaly

Background

Identification of Risk Factors. Identification of risk factors, predisposing conditions, and markers that confer increased risk for developing HF is an important part of the routine medical evaluation.[1] A number of conditions predispose to the development of HF,[2–12] and persuasive evidence exists that treatment of these risk factors decreases the likelihood of subsequent HF (see Guideline Section 3 for more details on risk factor modification and HF prevention). Although risk factors vary in the degree to which they are modifiable, detection of any risk factor identifies a patient in whom aggressive risk factor modification and more careful follow-up are warranted.

Method of Evaluation. Patients at risk for developing cardiac dysfunction should undergo careful history and physical examination to detect evidence of clinical HF and to uncover other conditions that predispose to HF. Appropriate therapies should be introduced to reduce the likelihood that left ventricular (LV) dysfunction will develop. Selected groups of high-risk patients and patients with signs and symptoms of HF should undergo echocardiographic examination to assess cardiac structure and function.[13] This initial examination may identify patients with cardiac dysfunction with or without symptomatic HF. These patients should undergo evaluation and treatment as defined in this guideline.

Echocardiography. The presence of certain risk factors makes the likelihood of underlying ventricular remodeling and dysfunction sufficiently likely to warrant diagnostic echocardiography (Table 4.2).

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Characterization of cardiac structure and function is critical for proper diagnosis, estimation of prognosis, and therapeutic decision-making. Contributions of cardiac dysfunction to the HF syndrome extend beyond the traditional view of simply quantifying LV systolic function (or left ventricular ejection fraction, LVEF), since the capacity and the efficiency of the LV also dictates the adequacy of stroke volume. This may explain why approximately 50% of patients with symptoms and signs of HF have a preserved LVEF.[14–17] Therefore, echocardiographic and Doppler assessment should include analysis of chamber sizes, valve function, LV mass and wall thickness, parameters of LV systolic and diastolic function, right ventricular (RV) systolic function, the presence of pulmonary hypertension, and the presence of pericardial disease. In patients whose echocardiographic imaging is unsatisfactory or when the degree of LVEF influences therapeutic decision making, other techniques such as radionuclide ventriculography, cardiac magnetic resonance imaging, or computed tomography may be used.

Recommendation

4.3 Routine determination of plasma B-type natriuretic peptide (BNP) or N-terminal pro-BNP (NT-proBNP) concentration as part of a screening evaluation for structural heart disease in asymptomatic patients is not recommended. (Strength of Evidence = B)

Background

Interest is high in developing markers of cardiac dysfunction that can be used to screen patients at risk for HF. Although initial data suggest that determination of BNP or NT-proBNP levels may be useful in this regard, data are insufficient to make a specific recommendation concerning their use for screening in a routine manner. The positive predictive value for these tests in a low-prevalence and asymptomatic population for the purpose of detecting cardiac dysfunction varies among studies, and the possibility of false positive results has significant cost-effectiveness implications.[18–23]

BNP is released by the heart in response to increased ventricular filling pressures, but may also be increased in the plasma as a result of ongoing myocardial dysfunction or hypertrophy. A low plasma BNP or NT-proBNP concentration has a high negative predictive value for cardiac dysfunction in patients presenting to the emergency room with dyspnea, and it may therefore be used to exclude HF as a cause of dyspnea with a relatively high degree of certainty.[24,25]

Evaluation of Patients Suspected of Having Heart Failure

Recommendation

4.4 Symptoms Consistent with HF. The symptoms listed in Table 4.3 suggest the diagnosis of HF. It is recommended that each of these symptoms be elicited in all patients in whom the diagnosis of HF is being considered. (Strength of Evidence = B)

Background

Symptoms. Thorough detection and evaluation of symptoms is critical in the assessment of patients suspected of having HF. The most common symptoms are dyspnea and fatigue from fluid retention, the inability to adequately augment cardiac output and oxygen delivery during exertion, or peripheral factors such as abnormal respiratory and skeletal muscle structure and function. These often manifest as exercise intolerance or a reduction in the intensity of usual activities. Signs of HF relate to manifestations of fluid retention. Dyspnea is typically noted during activity but may be severe enough to be present at rest. Dyspnea may be intermittent even when present at rest or manifest as periodic breathing (e.g., Cheynes-Stokes respiration).[26] Patients whose cardiac dysfunction evolves chronically may reduce their activity to minimize symptoms.[27] Comparing current activity level with exercise tolerance in the past may be helpful in detecting a decline in functional capacity. A patient's functional capacity should be judged with allowance for age and level of conditioning. Congestion may take many forms. Orthopnea and paroxysmal nocturnal dyspnea are symptoms of elevated left heart filling pressures that are more specific to underlying central congestion. These patients may or may not have visible edema. Peripheral edema occurs in the presence of elevated right-sided filling pressures, together with impaired renal handling of sodium and water. Significant volume overload typically is associated with substantial functional incapacity, yet patients may present with fatigue or exercise intolerance and manifest no signs of fluid retention. Symptoms may occur in isolation or not be classically related to physical signs. Nocturnal symptoms may predominate, whereas daytime symptoms, such as dyspnea on exertion, may be absent.

Less Common Presenting Symptoms. Patients may report nocturnal wheezing or cough, which can reflect fluid overload. In patients receiving angiotensin-converting enzyme (ACE) inhibitors, worsening cough should not be assumed to be drug-related, because it may be a manifestation of increasing left heart filling pressures (Section 7). Patients

Table 4.3. Symptoms Suggesting the Diagnosis of HF

Symptoms	Dyspnea at rest or on exertion
	Reduction in exercise capacity
	Orthopnea
	Paroxysmal nocturnal dyspnea (PND) or nocturnal cough
	Edema
	Ascites or scrotal edema
Less specific presentations of HF	Early satiety, nausea and vomiting, abdominal discomfort
	Wheezing or cough
	Unexplained fatigue
	Confusion/delirium
	Depression/weakness (especially in the elderly)

with severely decompensated cardiac failure may present with gastrointestinal symptoms representative of hepatic congestion or visceral edema, including early satiety, nausea, vomiting, and right upper quadrant pain.

Recommendation

4.5 Physical Examination. It is recommended that patients suspected of having HF undergo careful physical examination with determination of vital signs and careful evaluation for signs shown in Table 4.4. (Strength of Evidence = B)

Table 4.4. Signs to Evaluate in Patients Suspected of Having HF

Cardiac Abnormality	Sign
Elevated cardiac filling pressures and fluid overload	Elevated jugular venous pressure
	S3 gallop
	Rales
	Hepatojugular reflux
	Ascites
	Edema
Cardiac enlargement	Laterally displaced or prominent apical impulse
	Murmurs suggesting valvular dysfunction
Reduced cardiac output	Narrow pulse pressure
	Cool extremities
	Tachycardia with pulsus alternans
Arrhythmia	Irregular pulse suggestive of atrial fibrillation or frequent ectopy

Background

Elevation of the jugular venous pressure, hepatic enlargement or tenderness or pulsatility, and lower extremity edema are manifestations of elevated right heart filling pressures, associated with impaired renal sodium and water clearance.[28–31] They also can be due to hepatic or renal dysfunction, various hypo-oncotic states, as well as venous thromboembolism. If due to cardiac disorders, these findings may be accompanied by a loud pulmonic closure sound, RV heave, and a RV S3 (lower left sternal border) consistent with pulmonary hypertension. A prominent laterally displaced apical impulse is indicative of LV enlargement. Increased left heart filling pressure is suggested by rales, diminished breath sounds, wheezing, and an apical S3 gallop.[29]

Recommendation

4.6 It is recommended that BNP or NT-proBNP levels be assessed in all patients suspected of having HF, especially when the diagnosis is not certain. (Strength of Evidence = A)

Background

Two forms of natriuretic peptide, BNP and NT-proBNP, have been studied extensively as aids to establish the diagnosis, estimate prognosis, and monitor the response to therapy of patients with acute HF.[23,24,32,33]

Measurement of these peptides has been proposed in cases of acute dyspnea where the diagnosis of HF is uncertain, as evident from large, multicenter investigations.[23,24,33] The diagnostic accuracy of BNP, using a cutoff value of 100 pg/mL, was 83% relative to the assessment made by the independent cardiologists, whereas the negative predictive value of BNP for HF when levels were <50 pg/mL was 96%. As expected, measurement of BNP/NT-proBNP appeared to be most useful in patients with an intermediate probability of HF. Plasma NT-Pro BNP cut points of >450 pg/mL for patients younger than 50 years of age, >900 pg/mL for patients age 50-74 years of age, and >1800 pg/mL for patients 75 years or older were equally sensitive and specific for diagnosing HF; with <300 pg/mL providing 98% negative predictive value for ruling out HF.[23,33]

BNP was found to be predictive of HF when LV function was depressed or preserved, but cannot reliably distinguish between the two.[34] In patients with HF associated with preserved LVEF, the BNP cutoff value of 100 pg/mL still had a sensitivity of 86% and a negative predictive value of 96%.

BNP and NT-proBNP levels increase with age, more so in older women or in those with underlying renal insufficiency, in which case the same cutoff ranges may not provide the same degree of specificity for the diagnosis of HF, especially in elderly women with dyspnea.[35] However, BNP and NT-proBNP levels should be interpreted with some caution in patients with morbid obesity as they may have lower than expected plasma BNP/NT-proBNP levels.[36–38]

Recommendation

4.7 Differential Diagnosis. The differential diagnoses in Table 4.5 should be considered as alternative explanations for signs and symptoms consistent with HF. (Strength of Evidence = B)

Table 4.5. Differential Diagnosis for HF Symptoms and Signs

Myocardial ischemia
Pulmonary disease (pneumonia, asthma, chronic obstructive pulmonary disease, pulmonary embolus, primary pulmonary hypertension)
Sleep-disordered breathing
Obesity
Deconditioning
Malnutrition
Anemia
Hepatic failure
Chronic kidney disease
Hypoalbuminemia
Venous stasis
Depression
Anxiety and hyperventilation syndromes
Hyper or hypo-thyroidism

Background

A number of signs and symptoms of HF are nonspecific, particularly shortness of breath, which may reflect

underlying pulmonary disease or physical deconditioning.[26] Recognizing this lack of specificity is particularly important in a general practice setting where patients often present with noncardiac causes of shortness of breath or edema. In patients with dyspnea who do not present with clear signs of HF, the possibility of a pulmonary pathology, including pulmonary embolism, should be considered and evaluated. Spirometry, chest computed tomography, ventilation-perfusion lung scan, or pulmonary angiography should be performed as clinically indicated. It is important to recognize that sleep apnea and HF frequently coexist.[39–42] In patients with fatigue who are without clear signs of HF, physical deconditioning, sleep apnea, hypothyroidism, and depression should be considered as potential causes. Edema may be due to calcium channel blockers, other drugs (e.g. thiazolidinediones, non steroidal anti-inflammatory drugs [NSAIDs], pregabalin), hypoalbuminemia, or venous stasis.

Recommendations

4.8 It is recommended that patients with a diagnosis of HF undergo evaluation as outlined in Table 4.6. (Strength of Evidence = C)

Table 4.6. Initial Evaluation of Patients With a Diagnosis of HF

Assess clinical severity of HF by history and physical examination
Assess cardiac structure and function
Determine the etiology of HF, with particular attention to reversible causes
Evaluate for coronary disease and myocardial ischemia
Evaluate the risk of life-threatening arrhythmia
Identify any exacerbating factors for HF
Identify comorbidities which influence therapy
Identify barriers to adherence

4.9 Symptoms. In addition to symptoms characteristic of HF (dyspnea, fatigue, decreased exercise tolerance, fluid retention), evaluation of the following symptoms should be considered in the diagnosis of HF:

- **Angina**
- **Symptoms suggestive of embolic events**
- **Symptoms suggestive of sleep-disordered breathing**
- **Symptoms suggestive of arrhythmias, including palpitations**
- **Symptoms of possible cerebral hypoperfusion, including syncope, presyncope, or lightheadedness (Strength of Evidence = B)**

4.10 Functional Capacity/Activity Level. It is recommended that the severity of clinical disease and functional limitation be evaluated and recorded and the ability to perform typical daily activities be determined. This evaluation may be graded by metrics such as New York Heart Association (NYHA) functional class (Table 4.7) (Strength of Evidence = A) or by the 6-minute walk test. (Strength of Evidence = C)

Table 4.7. Criteria for NYHA Functional Classification in Patients With HF

Class I	No limitation of physical activity. Ordinary physical activity does not cause undue fatigue, palpitation, or dyspnea.
Class II	Slight limitation of physical activity. Comfortable at rest, but ordinary physical activity results in fatigue, palpitations, or dyspnea.
Class III	IIIA: Marked limitation of physical activity. Comfortable at rest, but less than ordinary activity causes fatigue, palpitation, or dyspnea. IIIB: Marked limitation of physical activity. Comfortable at rest, but minimal exertion causes fatigue, palpitation, or dyspnea.
Class IV	Unable to carry on any physical activity without discomfort. Symptoms of cardiac insufficiency present at rest. If any physical activity is undertaken, discomfort is increased.

4.11 Volume Status. The degree of volume excess is a key consideration during treatment. It is recommended that it be routinely assessed by determining:

- **Presence of paroxysmal nocturnal dyspnea or orthopnea**
- **Presence of dyspnea on exertion**
- **Daily weights and vital signs with assessment for orthostatic changes**
- **Presence and degree of rales, S3 gallop, jugular venous pressure elevation, hepatic enlargement and tenderness, positive hepatojugular reflux, edema, and ascites (Strength of Evidence = B)**

Background

Characteristic Symptoms. The presence or absence and severity of characteristic symptoms of HF, including those related to exercise tolerance and fluid overload, should be documented in all patients undergoing initial evaluation.

Comorbidities. Symptoms of comorbidities commonly associated with HF should be sought. These include angina,[43] symptoms of sleep-disordered breathing, presyncope, or syncope.

Physical Examination. The physical examination should focus on the detection and etiology of structural heart disease, current volume status, and the severity of HF, as a guide to initiating therapy and a baseline to gauge the effect of that therapy. Height and weight should be recorded. Supine and upright vital signs should be taken to assess for orthostasis. Presence of an S3 gallop and elevation of jugular venous pressure are invaluable specific markers of elevated cardiac filling pressures. A positive Kussmaul can be a flag for restrictive disease or significant HF.

Murmurs such as those of aortic stenosis or mitral regurgitation may provide clues to the etiology of LV dysfunction. Murmurs of tricuspid regurgitation and mitral regurgitation vary depending on the degree of pulmonary or systemic pressure, respectively, volume overload, ventricular dilatation, and failure of leaflet coaptation or elevated pulmonary pressures.

The physical examination has limitations. Pulmonary rales are an insensitive indicator of elevation in pulmonary

venous pressure, unless they occur abruptly.[27] Overt pulmonary edema rarely occurs where left heart filling pressure is chronically elevated, as the pulmonary vasculature adapts with increased lymphatic drainage. Ascites is common in patients with advanced HF (with contributing right HF), but it may be difficult to appreciate on physical examination. Although abdominal complaints can be misleading, history often is a better indicator of excess abdominal fluid than physical examination. Hepatojugular reflux is a sensitive indicator of volume expansion and may be demonstrated in states of RV dysfunction.[31]

Functional Assessment. Determination of baseline exercise and functional limitation is important during the initial evaluation of patients with established HF. Decisions regarding hospitalization and response to medications and other interventions are aided by estimation of the degree of limitation present at the first evaluation.

A number of strategies can be employed to assist in these estimates, including 6-minute walk test distance.[44] One common, time-tested, and simple metric is the NYHA functional classification, which is shown in Table 4.7. [45] Although NYHA class is subjective, numerous longitudinal studies have shown the prognostic power of this determination, and serial evaluation is helpful to gauge response to therapy. Therapeutic recommendations often are directed toward patients within particular NYHA classes, based on use of this indicator as an entry criterion for clinical trials. Success of therapy may be indicated by improvement of at least 1 functional class.[46–49]

Recommendations

4.12 Standard Laboratory Tests. It is recommended that the following laboratory tests be obtained routinely in patients being evaluated for HF: serum electrolytes, blood urea nitrogen, creatinine, glucose, calcium, magnesium, fasting lipid profile (low-density lipoprotein cholesterol, high-density lipoprotein cholesterol, triglycerides), complete blood count, serum albumin, uric acid, liver function tests, urinalysis, and thyroid function. (Strength of Evidence = B)

4.13 Electrocardiogram (ECG). It is recommended that all patients with HF have an ECG performed to:
- **assess cardiac rhythm and conduction (in some cases, using Holter monitoring or event monitors)**
- **assess electrical dyssynchrony (wide QRS or bundle branch block), especially when LVEF <35%**
- **detect LV hypertrophy or other chamber enlargement**
- **detect evidence of myocardial infarction (MI) or ischemia**
- **assess QTc interval, especially with drugs that prolong QT intervals (Strength of Evidence = B)**

4.14 Chest X-Ray. It is recommended that all patients with HF have a postero-anterior and lateral chest X-ray examination for determination of heart size, evidence of fluid overload, detection of pulmonary and other diseases, and appropriate placement of implanted cardiac devices. (Strength of Evidence = B)

4.15 Additional Laboratory Tests. It is recommended that patients with no apparent etiology of HF or no specific clinical features suggesting unusual etiologies undergo additional directed blood and laboratory studies to determine the cause of HF. (Strength of Evidence = B)

Background: Initial Diagnostic Testing

Electrocardiogram and Chest X-Ray. The electrocardiogram (ECG) provides important information on acute ischemia, prior MI, conduction abnormalities, arrhythmias, and ventricular hypertrophy.[50] A chest radiograph may show evidence for cardiac chamber enlargement, increased pulmonary venous pressure, interstitial or alveolar edema, pleural effusions, valvular or pericardial calcification, or coexisting lung disease.

Laboratory Evaluation. The complete blood count may show anemia.[51,52] Hyponatremia, from free water retention, may reflect elevated serum vasopressin levels and activation of the renin-angiotensin system.[53,54] Hyponatremia, which has been associated with poor prognosis,[55,56] may also result from excessive diuresis, but more often indicates severe HF with excess total body salt and water. Elevated serum creatinine may not only reflect important underlying renal impairment but may also represent a prerenal state from reduced cardiac output, venous congestion, intraabdominal hypertension or excessive diuresis.[57–59] Renal dysfunction is associated with a worse prognosis.[60–63] Prerenal azotemia is usually associated with a disproportionate increase in blood urea nitrogen. If creatinine is disproportionately elevated, it generally indicates intrinsic renal disease. Hypoalbuminemia contributes to low plasma oncotic pressure and edema formation. An abnormal urinary sediment may suggest glomerular disease or infection, and proteinuria may play a role in low oncotic pressure and edema formation. Hyper- or hypothyroidism can precipitate or aggravate ventricular dysfunction and clinical HF and may be clinically occult in the elderly. A lipid profile is valuable in patients with significant risk factors for or a documented history of coronary artery disease.

Determination of Etiology. Initial assignment of HF etiology should be as specific as possible. Significant differences in prognosis are commonly noted among the various etiologies of HF, and identification of specific etiologies, such as ischemic heart disease, may trigger specific directions for evaluation and treatment (Section 13). A number of common etiologies dominate the causes of HF in most practice settings. Ischemic heart disease remains a common cause, especially among patients with reduced LVEF.[43]

Background: Common Etiologic Factors

Coronary Artery Disease. Patients with evidence of a MI, coronary artery bypass graft surgery, or percutaneous angioplasty or patients who have coronary artery narrowing of greater than 70% in at least 1 artery are most likely to have an ischemic cardiomyopathy.[64] On the other hand, the mere presence of atherosclerotic coronary artery disease may not necessarily explain the underlying etiology if cardiac dysfunction is out of proportion to the degree of coronary artery disease. Patients with initially established non-ischemic cardiomyopathy can also develop progressive coronary artery disease, leading to adverse clinical outcomes, such as sudden cardiac death.

Hypertension. Population-based analyses have shown hypertension to be the most important population-attributable risk for HF.[5,65] Hypertensive or previously hypertensive patients with a non-dilated left ventricle, preserved LVEF, left atrial enlargement, and concentric LV hypertrophy are most likely to have hypertension as the principal etiology for HF. Among all hypertensive patients with HF, elevated blood pressure should be presumed to contribute to both the cardiovascular pathology and ongoing clinical manifestations of the disease.

The assignment of hypertension as an etiology, particularly of LV systolic dysfunction, has been challenged of late. Clearly, hypertension often is associated with ischemic heart disease and typically is not considered primary in these cases. Documentation of the presence of hypertension may be difficult in many cases of apparently idiopathic cardiomyopathy unless the medical history is carefully reviewed. Many patients with a history of hypertension will not be hypertensive when presenting with systolic dysfunction. Likewise, hypertension may emerge as ventricular function improves with institution of proper medical therapy. In any event, close observation for the development of hypertension is warranted during follow-up.

Alcoholic Cardiomyopathy. Careful history should be directed to determining the quantity of alcohol consumption. In the absence of a clear alternative, an alcoholic etiology is likely among patients with a dilated left ventricle and history of consuming excessive amounts of alcohol.

Valvular Disease. In patients with chronic valvular disease, physical findings may not be characteristic because of low cardiac output. This is especially true of patients with ''low gradient aortic stenosis.'' A history of known valvular or rheumatic heart disease should be sought. Detection of occult valvular disease is one reason for the importance of routine echocardiography as part of the evaluation process.

Idiopathic and Familial Dilated Cardiomyopathy. A number of patients have no apparent cause for their HF despite careful clinical evaluation. The label idiopathic cardiomyopathy represents a diagnosis of exclusion, and less common causes should be sought as indicated below. A family history of cardiomyopathy should be solicited, especially if non-ischemic cardiomyopathy is associated with conduction system disease and arrhythmias. A finding of idiopathic cardiomyopathy might warrant cardiovascular testing in first- and second-degree relatives.[66–68] Apical ballooning (''tako-tsubo'') cardiomyopathy is a transient syndrome with profound anteroapical dysfunction of unclear etiology and associated with emotional stress or high catecholamines surge. Table 4.8 lists physical and laboratory findings that can point to less common etiologies.

Table 4.8. Physical Examination Findings Related to Etiology

Physical Examination	Findings and Implications
Skin	Pigmentation: iron overload
	Lipid deposits: hyperlipidemia
	Spider angiomata: liver disease
	Easy bruisability, nail pitting, amyloidosis
	Cushingoid features: glucocorticoid excess
	Skin laxity: pseudoxanthoma elasticum
	Rash: pellagra
	Malar rash of discoid: lupus
	Sclerodactyly or skin tightening: CREST or scleroderma
Lymph nodes	Adenopathy: sarcoidosis; lymphoma
Thyroid	Modularity enlargement: hyper- or hypothyroidism
Jugular veins	Kussmaul sign: constriction or restriction
Heart rate	Resting tachycardia: a very rapid ventricular response to atrial fibrillation or persistent tachyarrhythmia may suggest a tachycardia-induced cardiomyopathy
Carotids	Delayed upstroke: aortic stenosis
	Bifid carotid contour: may suggest hypertrophic cardiomyopathy
	Carotid bruits may suggest associated atherosclerotic disease
Cardiac palpation	Hyperdynamic, laterally displaced apical impulse: LV volume overload (aortic or mitral regurgitation),an adynamic point of maximal impulse suggests a dilated cardiomyopathy. These displaced PMI findings are usually accompanied by an S3 gallop
Cardiac auscultation	Murmurs: specific valvular pathologies of aortic stenosis, aortic regurgitation, mitral stenosis and mitral regurgitation may be present indicating the potential etiology. Elevation of diastolic pressures may lessen traditional murmurs of regurgitation and low cardiac output may lessen traditional murmurs of stenosis
	Diastolic knock: pericardial disease
	Diastolic plop: thrombus or atrial myxoma
Extremities	Cyanosis: may be a manifestation of extreme low output state or right to left shunting through a congenital defect
	Bounding peripheral pulse and a Quincke's sign: suggest wide pulse pressure and may be clues to hyperthyroidism, aortic regurgitation, AV fistula
	Warm extremities and high cardiac output: beriberi, hyperthyroidism

Familial Hypertrophic Cardiomyopathy. Hypertrophic cardiomyopathy is an autosomal dominant condition with both genotypic and phenotypic variability, and patients with this condition may present with dyspnea or syncope.

Echocardiography is an effective diagnostic approach. Genetic testing is often indicated.[68]

Peripartum Cardiomyopathy. HF occurring 1 month before or within 5 months of delivery, with no prior patient history of heart disease or other etiology of cardiomyopathy, is generally labeled peripartum cardiomyopathy.

Chagas Cardiomyopathy. In patients from Latin America presenting with electrocardiographic and echocardiographic manifestations of ''ischemic'' cardiomyopathy, but who are found to have no significant coronary artery disease on angiography, the diagnosis of Chagas cardiomyopathy should be considered, and Trypanosoma Cruzi titers checked, if they come from an endemic region (e.g., Central or South America).

Endocrine Abnormalities. Pheochromocytoma should be considered in patients with hypertension that is particularly difficult to manage or is characterized by severe fluctuations in blood pressure. Because hypo- or hyperthyroidism can exacerbate HF and, on rare occasion, can represent the principal cause of HF, thyroid-stimulating hormone should be measured. Acromegaly is a rare, but well-recognized, finding in cardiomyopathy and may be uncovered by obtaining a history of increase in jaw, hand, or foot size, or by comparison of the patient's current features with dated photographs. Diabetes mellitus is commonly associated with the development of HF, especially in those with microvascular diseases such as retinopathy or microalbuminuria.[69] Diabetes mellitus can contribute directly to the development of HF, via its role as a risk factor for coronary artery disease, or secondary to diabetic agents such as thiazolidinediones that cause fluid retention (see Section 3 for a full discussion of the contribution of diabetes to the development of HF).

Cardiotoxin Exposure. Anthracyclines and occasionally other anti-cancer agents may result in cardiomyopathy, depending on the dose received.[70,71] In rare cases, sulphur containing drugs and a number of other agents, including some antibiotics, may initiate an allergic inflammatory reaction leading to eosinophilic myocarditis and decline in heart function.[72] Dating the onset of HF to the initiation of these agents will be helpful.

Radiation Therapy. Chest radiation can affect all cardiac structures, including the pericardium, myocardium, coronary arteries and heart valves, and result in a constrictive/restrictive cardiomyopathy, valvular heart disease and/or ischemic heart disease. Ideally, evaluation and management of radiation-induced heart disease should involve a HF specialist and/or cardiac surgeon with expertise in cardio-oncology.[73]

Exposure to Illicit Drugs. The use of stimulant drugs such as cocaine and methamphetamine may lead to the development of HF.[74–77] Patients should be educated on the cardiovascular risks of using these agents.

Drugs Associated With HF Exacerbation. Some pharmacologic agents, including selected calcium channel blockers and antiarrhythmics, may depress cardiac function and increase the likelihood of HF or exacerbation of preexistent or subclinical heart dysfunction.[78,79] NSAIDs have been associated with an increased risk of HF hospitalization, and they should be recognized as a causative factor for HF exacerbation and avoided in these patients.[80] Thiazelinediones and pregabalin are also associated with fluid retention in patients with HF, and they are not recommended in patients with symptomatic HF.[81,82] Tumor necrosis factor antagonists have also been associated with new onset and/or exacerbation of existing HF.[83]

Connective Tissue Disorders. Systemic lupus erythematosus, scleroderma, and other connective tissue disorders may represent a cause of HF. Vasculitis, hypertension, systemic lupus erythematosus, pericardial involvement, and renal impairment all may contribute to the syndrome of HF. Scleroderma may be associated with myocardial fibrosis with restrictive physiology. In the presence of characteristic skin changes, arthritis, or other organ system involvement, serum antinuclear antibody and rheumatoid factor should be measured.

Toxin Exposure. Lead, arsenic, and cobalt are three toxins that may cause progressive myocardial dysfunction. A history of consumption of lead paint or drinking of well water may provide clues to this unusual cause.

Myocarditis (see also section 16). Rapidly progressive cardiomyopathy, including a rapidly deteriorating clinical condition, should raise suspicion of active myocarditis, including giant cell myocarditis, and represents an indication for consideration of endomyocardial biopsy.[84] Myocarditis may be characterized with a subclinical onset or gradual deterioration. Hepatitis C or HIV infection may be a cause of myocarditis, and there should be a low threshold for measurement of viral serology.[85–88]

Nutritional Deficiencies. Beriberi (thiamine deficiency) may appear in individuals on fad diets or those hospitalized in intensive care units receiving inadequate nutrition. Patients with protein-losing enteropathy due to right HF may develop thiamine deficiency. Selenium deficiency has been recognized as a potential etiology.

Amyloidosis. HF with preserved LVEF and minimal or no LV dilatation, coupled with increased LV and RV wall thickness by echocardiogram, despite normal or diminished QRS voltage on ECG, should raise suspicion of amyloidosis.[89] Serum and urine immunoelectrophoresis should be performed, along with measurement of serum free light chains, and confirmation with endomyocardial biopsy (and in some cases genotyping) may be warranted to determine the presence and subtype of amyloidosis involved as they may have different prognosis and management strategies. In particular, specific testing for the presence of transthyretin

deposition (familial or wild-type) may identify subtypes that are amenable to transplantation considerations. Cardiac magnetic resonance imaging (MRI) can also aid with the diagnosis and prognosis of cardiac amyloidosis.

Hemoglobinopathies. Repeated transfusions from chronic hemolytic anemia may result in iatrogenic iron overload.

High Output States. Hyperthyroidism, arteriovenous (AV) malformations (rarely), large AV fistulas used for dialysis, or sepsis may result in severe volume overload and high output failure, characterized by preserved LVEF with increased ventricular volumes. HF related to sepsis and other critical acute illnesses is usually a result of transient LV dysfunction that is often self-resolving.

Tachycardia Mediated Cardiomyopathy. Several types of tachycardias including ectopic atrial tachycardia, permanent junctional reciprocating tachycardia (PJRT) using an accessory pathway, atrial fibrillation with a rapid ventricular response, incessant idiopathic ventricular tachycardias, and frequent premature ventricular beats have been associated with the development of a reversible dilated cardiomyopathy. Although conclusive studies are lacking to determine the upper limit of heart rate that may be associated with the development of a cardiomyopathy, a general consensus is that persistent tachycardia >110 beats per minute is required to induced cardiomyopathy. In addition, frequent premature ventricular contractions (PVCs) (20-30% of all beats or $>10{,}000$ per 24 hour)[90,91] may also be associated with the development of cardiomyopathy.[92,93] The optimal level of rate control to prevent the development of cardiomyopathy in patients with atrial fibrillation is not known. In general, a resting ventricular response of 60 to 80 beats per minute and a ventricular response between 90-115 beats per minute during moderate exercise have been suggested.[94] The AFFIRM (Atrial Fibrillation Follow-up Investigation of Rhythm Management) trial targeted heart rates of $\leq$80 bpm at rest, $\leq$110 bpm during a 6 minute walk test, or an average heart rate of 100 beats per minute over at least 18 hours of continuous ambulatory monitoring.[95]

Sarcoidosis. Sarcoid can mimic many things; it commonly is associated with conduction abnormalities and ventricular tachyarrhythmias. Hilar lymphadenopathy may be a clue to the diagnosis of sarcoidosis. It can be confirmed by endomyocardial biopsy, although false negatives are frequent and a negative biopsy does not exclude a diagnosis of sarcoidosis. Cardiac MRI or specialized positron emission tomography − computed tomography (PET-CT) protocols may help to determine the presence of inflammation.

Hemochromatosis. In the setting of dilated cardiomyopathy, darkened skin, and diabetes, hemochromatosis should be excluded using ferritin. In acute inflammatory states, when ferritin is elevated, other tests, such as iron, iron saturation, and total iron-binding capacity, may be considered. Cardiac MRI may provide reliable accuracy in determining cardiac involvement of iron deposition.

Recommendations

4.16 Evaluation of myocardial ischemia is recommended in those who develop new-onset LV systolic dysfunction especially in the setting of suspected myocardial ischemia or worsening symptoms with pre-existing CAD. The choice of testing modality should depend on the clinical suspicion and underlying cardiac risk factors. Coronary angiography should be considered when pre-test probability of underlying ischemic cardiomyopathy is high and an invasive coronary intervention may be considered. (See Section 13 for specific clinical situations and Strength of Evidence)

4.17 Exercise testing for functional capacity is not recommended as part of routine evaluation in patients with HF. Specific circumstances in which maximal exercise testing with measurement of expired gases should be considered include:

- **Assessing disparity between symptomatic limitation and objective indicators of disease severity**
- **Distinguishing non HF-related causes of functional limitation, specifically cardiac versus pulmonary**
- **Considering candidacy for cardiac transplantation or mechanical circulatory support**
- **Determining the prescription for cardiac rehabilitation**
- **Addressing specific employment capabilities (Strength of Evidence = C)**

Background

Treadmill exercise testing, with or without measurement of oxygen uptake, to assess functional capacity is not routinely required in the evaluation of patients with a known diagnosis of HF. Nevertheless, there are a number of clinical circumstances in which such testing is beneficial.[96] Exertional dyspnea and exercise intolerance may be due to noncardiac causes, especially pulmonary. When there is a disparity between symptoms and objective findings of HF, exercise testing with measurement of expired gases to determine peak oxygen consumption may be useful.

Measurement of peak oxygen uptake may be of assistance in determining candidacy for cardiac transplantation by quantifying functional limitation and adding prognostic information.[97] There is no uniform agreement on a cutoff in peak oxygen uptake that constitutes an absolute criterion for candidacy for transplantation. A value of <10 mL O_2 kg/min denotes severe functional incapacity and poor prognosis, whereas a value of <14 mL O_2 kg/min indicates a patient with underlying advanced HF in whom advanced therapeutic options such as transplantation or ventricular assist devices may be considered.[98] The test should be

performed after optimizing medical therapy. Several studies suggest that measuring peak oxygen uptake may be less useful in predicting prognosis in patients on beta blockers.[99,100] It is commonly recognized that women have lower peak oxygen uptake than men. In younger individuals (<50 years of age) and women, percent of predicted peak VO_2 $\leq 50\%$, or a minute ventilation equivalent of carbon dioxide production slope (VE/VCO_2) of >35 are also indicators of poor prognosis and can be considerations for transplant candidacy.[98] In obese subjects a calculation of VO_2 by lean body mass may also be helpful.[98]

Common Errors in Initial Assessment

General History. Historical information should be well-documented wherever possible. For example, electrocardiographic or enzyme evidence of prior MI should be reviewed, rather than relying on the patient's description of the event. Early symptoms of HF, such as cough and rales, often are incorrectly attributed to respiratory infection. Specific evidence should be sought to confirm or refute the diagnosis.

Physical Examination. There are a number of ways in which the patient's volume status may be misjudged. Rales may be due to pulmonary disease, rather than pulmonary edema. Conversely, severe chronic volume overload may occur in the absence of pulmonary rales. Edema may be due to venous stasis disease or medications such as calcium channel blockers, rather than volume overload. Assessment of jugular venous pressure and its wave form is invaluable in the accurate assessment of volume status. However, the absence of evidence of volume overload on examination does not exclude the possibility of severe functional impairment related to HF. In addition, patients may have volume expansion and yet not manifest rales on chest examination. Cardiac murmurs may vary significantly depending upon the patient's volume status. Decreased murmur intensity may be due to elevated filling pressures or low cardiac output.

Recommendation

4.18 Routine endomyocardial biopsy is not recommended in cases of new-onset HF. Endomyocardial biopsy should be considered in patients with rapidly progressive clinical HF or ventricular dysfunction, despite appropriate medical therapy. Endomyocardial biopsy also should be considered in patients suspected of having myocardial infiltrative processes, such as sarcoidosis or amyloidosis, or in patients with malignant arrhythmias out of proportion to LV dysfunction, where sarcoidosis and giant cell myocarditis are considerations. (Strength of Evidence = C)

Background

In patients who present with rapidly progressive signs and symptoms of HF and ventricular dysfunction (often associated with a dilated left ventricle and new ventricular arrhythmias or conduction abnormalities) and are poorly responsive to appropriate medical therapy, the diagnosis of giant cell myocarditis should be considered. Retrospective data suggest that this disease is associated with high mortality rates and that it may respond to immunosuppression.[84,101] Clinical trials performed in patients with more common forms of lymphocytic myocarditis have failed to demonstrate a clinical benefit from immunosuppressive therapy, and these patients have a high rate of spontaneous recovery.[102,103] Other clinical scenarios that may warrant considerations for endomyocardial biopsy including suspicion for eosinophilic/hypersensitivity myocarditis or drug-induced cardiomyopathy, and the confirmation of infiltrative cardiomyopathies, such as amyloidosis (systemic or transyretin) or sarcoidosis, or suspected forms of cardiomyopathies, such as glycogen storage disease. [104]

Follow-Up Evaluation

Recommendation

4.19 It is recommended that clinical evaluation at each follow-up visit include determination of the elements listed in Table 4.9. (Strength of Evidence = B).

These assessments should include the same symptoms and signs assessed during the initial evaluation. (Strength of Evidence = B)

Table 4.9. Elements to Determine at Follow-Up Visits of HF Patients

Functional capacity and activity level
Changes in body weight
Patient understanding of and adherence with dietary sodium restriction
Patient understanding of and adherence with medical regimen
History of arrhythmia, syncope, presyncope, palpitation or ICD discharge
Adherence and response to therapeutic interventions
The presence or absence of exacerbating factors for HF, including worsening ischemic heart disease, hypertension, and new or worsening valvular disease

Background

Volume Assessment. Determination of serial changes in volume status is a critical part of the follow-up of the patient with HF. Ongoing efforts to achieve diuresis may be underway as part of the management plan. Diuretic therapy can be difficult to adjust, and identifying the optimal maintenance dose can be challenging. States of persistent fluid overload or excessive weight loss are common. Restriction of dietary sodium intake is a key factor in optimizing fluid balance. Improved adherence to dietary sodium restriction may result in significant negative fluid balance, mandating adjustment of diuretic therapy.

Pharmacologic Therapy. The difficulty associated with maintaining an appropriate pharmacologic regimen in patients with HF is well known, even when the patient has experienced clinical benefit from specific medications. Economic factors, polypharmacy, side effects, and

misperceptions concerning the relationship of medications to specific somatic feelings all limit adherence with chronic medical regimens. Careful review of current medications may uncover lack of adherence and also detect use of over-the-counter medications that may be detrimental.

Recommendation

4.20 In the absence of deteriorating clinical presentation, repeat measurements of ventricular volume and LVEF should be considered in these limited circumstances:

- **When a prophylactic implantable cardioverter defibrillator (ICD) or cardiac resynchronization therapy device and defibrillator (CRT-D) placement is being considered in order to determine that LVEF criteria for device placement are still met after medical therapy (Strength of Evidence = B)**
- **When patients show substantial clinical improvement (for example, in response to beta blocker treatment or following pregnancy in patients with peripartum cardiomyopathy). Such change may denote improved prognosis, although it does not in itself mandate alteration or discontinuation of specific treatments (see Section 7). (Strength of Evidence = C)**
- **In alcohol and cardiotoxic substance abusers who have discontinued the abused substance. (Strength of Evidence = C)**
- **In patients receiving cardiotoxic chemotherapy. (Strength of Evidence = B)**

Repeat determination of LVEF is usually unnecessary in patients with previously documented LV dilatation and low LVEF who manifest worsening signs or symptoms of HF, unless the information is needed to justify a change in patient management (such as surgery or device implantation). (Strength of Evidence = C)

Background

Follow-Up Assessment of Ventricular Function. There generally is no reason for repeat echocardiography unless it is anticipated that findings will prompt a change in therapy. There is no evidence that changes in LV volume or LVEF warrant modifications in therapy with drugs such as ACE inhibitors or beta blockers. However, the substantial improvement or normalization in LV volumes and LVEF often seen with beta blocker treatment is associated with improved prognosis, and patients deserve this information. It is reasonable to consider repeat echocardiography for this purpose at least 3 or more months after initiation of beta blockade, particularly if the patient has manifested improvement in signs and symptoms of HF.

In patients with previously documented ventricular dilatation and reduced LVEF, repeat measurement should be considered if the finding of further reduction in LVEF is likely to prompt additional treatment. A good example is the patient manifesting progressive signs and symptoms of HF who might be listed for cardiac transplantation if further worsening of LVEF is not prevented.

Recommendation

4.21 It is recommended that reevaluation of electrolytes and renal function occur at least every 6 months in clinically stable patients and more frequently following changes in therapy or with evidence of change in volume status. More frequent assessment of electrolytes and renal function is recommended in patients with severe HF, those receiving high doses of diuretics, those on aldosterone antagonists, and those who are clinically unstable. (Strength of Evidence = C)

See Section 7 for recommendations for patients on an aldosterone receptor antagonist.

Background

The approach to laboratory assessment during follow-up must be individualized. Circumstances requiring more frequent monitoring of renal function and electrolytes include severe HF, changes in volume status or worsening signs and symptoms of HF, diabetes, prescription of an aldosterone antagonist, and initiation or active adjustment of ACE inhibitors or diuretics. Moderate to severe renal dysfunction is common in patients with HF and reduced LVEF and in patients with HF and preserved LVEF, and it may be associated with hyperkalemia. Diabetics, elderly and patients with chronic renal insufficiency are at particular risk for hyperkalemia and require more frequent laboratory monitoring during follow-up.

The role of serial measurements of cardiac biomarkers remains controversial, although some studies have suggested that sequential monitoring may provide useful risk prediction,[105] even though the precise test ranges and frequencies have not yet been established.[106] The role of BNP and NT-proBNP in risk stratification has been very consistent, although the majority of studies have demonstrated the value of a single-point measurement as it relates to long-term outcomes. The STARS-BNP (Systolic Heart Failure Treatment Supported by BNP) study demonstrated a significant reduction in HF death or HF hospitalization for patients randomized to BNP-guided therapy.[107] Other studies of biomarker-guided therapeutic management of HF have not demonstrated improved clinical outcomes associated with this approach as compared to standard clinical management, although some benefits have been found in specific subgroups such as those <75 years of age and in patients whose NT-proBNP were consistently below target levels during follow-up.[108,109] The incremental value of serial BNP testing *solely* for the purpose of risk stratification has not been established.

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Section 5: Management of Asymptomatic Patients with Reduced Left Ventricular Ejection Fraction

Overview

Left ventricular (LV) remodeling and reduced ejection fraction (EF) should be distinguished from the syndrome of clinical heart failure (HF). When LVEF is reduced (<40%), but there are no signs and symptoms of HF, the condition frequently is referred to as asymptomatic LV dysfunction (ALVD). It is important to distinguish between ALVD and patients categorized as New York Heart Association (NYHA) Class I HF. Although patients with NYHA Class I HF do not currently have HF symptoms, they may have ALVD currently, or they may have clinical systolic HF with symptoms in the past. In contrast, patients with ALVD have no past history of HF symptoms. It is now well recognized that there may be a latency period when the LVEF is reduced before the development of symptomatic HF. Although most attention in the HF literature has centered on patients with symptoms, evidence now indicates that ALVD is more common than previously assumed. The recent realization that therapies aimed at symptomatic HF may improve outcomes in patients with ALVD has increased the importance of recognizing and treating patients with this condition.

Prevalence. The prevalence of systolic ALVD ranges from 6% to 16% in population-based studies.[1–4] The prevalence of ALVD was 16.7% among a cohort of 1046 asymptomatic diabetic patients without known coronary artery disease.[5] Some studies suggest that patients with ALVD equal or outnumber those with overt HF. The First National Health and Nutrition Examination Survey Epidemiologic Follow-up Study (NHANES I) reported only a 2% prevalence of overt HF in individuals ages 25 to 74 years, though this value likely is an underestimate.[6] The prevalence of both ALVD and overt HF dramatically increase with age. The lifetime risk of developing HF is approximately 20% in octogenarians.[7–9] In specific populations, such as those who have received cardiotoxic agents and those screened due to a family history of dilated cardiomyopathy, the incidence of ALVD is likely much higher.

Prognosis. Patients with ALVD have approximately half the mortality rate (5% annualized) of those with overt symptoms of HF, but their risk of death is 5 to 8 times higher than a normal age-matched population. In the Study of Left Ventricular Dysfunction (SOLVD) prevention study, patients with untreated ALVD developed overt HF at a 10% annual rate, with a further 8% annual risk of death or hospitalization for HF.[10] These data indicate patients with ALVD are at high risk for developing HF. The majority of data regarding outcomes in patients with ALVD come from the SOLVD-prevention study; it would be valuable to have more recent data to fully understand the mortality risk of ALVD in the current era.

One trial that can be used to evaluate ALVD outcomes in the current era is the Occluded Artery Trial (OAT).[11] The study enrolled 2216 subjects 3−28 days post-myocardial infarction (MI) with mean LVEF 48% (LVEF <40% in 21% of the study population). The large majority of subjects (83%) were asymptomatic. A high proportion of subjects received multiple drug therapies including >80% treated with beta blockers, angiotensin converting enzyme (ACE) inhibitors or angiotensin receptor blockers (ARB), statins, and aspirin. Subjects were randomly assigned to a percutaneous coronary intervention (PCI) strategy to open the infarct-related artery or medical management. During a mean follow-up period of 1059 days, adverse cardiac event rates (all-cause mortality, non-fatal MI, and HF hospitalization) were much lower than that reported in the SOLVD study population (301 events with calculated crude event rate 4.8 per 100 patient-years). There were no significant differences in rates of adverse outcome events in the two treatment groups. Lower cardiac event rates in the OAT study population may be attributable to less severe systolic dysfunction and more widespread use of post-MI medical therapies.

Managing Patients With ALVD. The management of patients with ALVD focuses on cardiovascular risk factors and on preventing, controlling, or reducing progressive ventricular remodeling.

A number of risk factors have the potential to promote progression of ventricular remodeling and adverse outcomes in patients with ALVD. These include systemic hypertension, coronary artery disease, diabetes, obesity, and metabolic syndrome.[6,12–15] Population-attributable risk for hypertension and MI may be as high as 60% to 70%, underscoring the importance of preventing and managing these two conditions.[12,13,16–18] The 30% or more of patients with ALVD who do not have ischemic heart disease may suffer from hypertension, diabetes mellitus, alcohol overuse, or familial or idiopathic dilated cardiomyopathy. Surveillance studies suggest that relatives of those with idiopathic dilated cardiomyopathy often have asymptomatic LV dilatation and may be at increased risk for developing HF.[19,20] In addition, those exposed to toxins through alcohol overuse, ionizing radiation, or chemotherapy with anthracyclines may develop ALVD, which may progress to HF in the absence of intervention.[21]

Recommendations

5.1 It is recommended that all patients with ALVD exercise regularly according to a physician-directed prescription to avoid general deconditioning; to optimize weight, blood pressure, and diabetes control; and to reduce cardiovascular risk. (Strength of Evidence = C)

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5.2 Smoking cessation is recommended in all patients including those with ALVD. (Strength of Evidence = B)

5.3 Alcohol abstinence is recommended if there is current or previous history of excessive alcohol intake. (Strength of Evidence = C)

5.4 It is recommended that all patients with ALVD with hypertension achieve optimal blood pressure control. (Strength of Evidence = B)

Background

Therapeutic Approaches. Cardiovascular risk factor reduction is advocated in patients with ALVD to decrease the risk of developing overt HF. Control of blood pressure and treatments that slow the progression of ischemic heart disease may have substantial benefit. (See Section 3 for more on the control of cardiovascular risk factors.)

Recommendation

5.5 ACE inhibitor therapy is recommended for asymptomatic patients with reduced LVEF (<40%). (Strength of Evidence = A)

Background

A twelve-year follow up in SOLVD demonstrated that the initial benefit of enalapril was maintained.[10] Survival curve analysis has confirmed an absolute 9.2-month benefit in life expectancy conferred by 40 months of treatment with an ACE inhibitor, a benefit conferred despite the fact that nearly all patients enrolled in SOLVD went on to receive ACE inhibitors after termination of the randomized portion of the trial. The likelihood of death after 12 years in the treatment group remained fairly constant at approximately 5% annually.

A substudy of the SOLVD trial found that administration of enalapril reduced the tendency to progressive LV enlargement in patients with ALVD.[22] This beneficial effect on LV remodeling, in combination with prevention of MI, most likely explains the mechanism of reduction of both cardiovascular mortality and progression to HF observed in the SOLVD Prevention trial.[23–25] Thus ACE inhibitors are indicated in patients with reduced LVEF, regardless of symptoms.

Recommendation

5.6 ARBs are recommended for asymptomatic patients with reduced LVEF who are intolerant of ACE inhibitors from cough or angioedema. (Strength of Evidence = C)

Routine use of the combination of ACE inhibitors and ARBs for prevention of HF is not recommended in this population. (Strength of Evidence = C)

Background

Randomized clinical trials of ARBs in asymptomatic patients with LV systolic dysfunction who are intolerant of ACE inhibitors have not been conducted. Despite the absence of definitive data, based on the results of the Candesartan in Heart Failure Assessment of Reduction in Mortality and Morbidity (CHARM)-Alternative and the Valsartan Heart Failure Trial (Val-HeFT) and a variety of pathophysiologic and clinical considerations, it is reasonable to use an ARB in a patient with ALVD if the patient is intolerant to an ACE inhibitor.[26,27] The addition of an ARB to an ACE inhibitor in asymptomatic patients with reduced LVEF has not been investigated.

Recommendation

5.7 Beta blocker therapy should be considered in asymptomatic patients with reduced LVEF. (post-MI, Strength of Evidence = B; non post-MI, Strength of Evidence = C)

Background

Ischemic Heart Disease With ALVD. A strong rationale exists for the use of beta blocker therapy in the management of patients with ALVD from ischemic heart disease, based on the benefits seen in patients with cardiac dysfunction and no overt HF after acute MI. The Carvedilol Post-Infarct Survival Control in Left Ventricular Dysfunction (CAPRICORN) study examined the effects of carvedilol in asymptomatic patients with reduced LVEF after MI, with concomitant use of ACE inhibitors, aspirin, and statins in the majority of patients. Although there was no difference between the carvedilol and placebo groups in the number of patients meeting the primary endpoint of all-cause mortality or hospital admission, carvedilol use was associated with fewer deaths, as well as a reduction in the combined endpoint of death or recurrent MI, classical end points in previous studies of beta blockade after MI.[28]

Beta blockade has been shown to attenuate LV remodeling in patients with ALVD. The Reversal of Ventricular Remodeling with Toprol-XL (REVERT) Trial randomized 149 patients to metoprolol succinate 50 mg, 200 mg, or placebo for 12 months. LV end-systolic volume, end-diastolic volume, and LVEF were measured at baseline and 6 and 12 months. Patients randomized to metoprolol succinate 200 mg had a significant decrease in LV end-systolic volume index and a significant increase in LVEF as compared to baseline and placebo at 12 months.[29] Approximately half of the patients in REVERT had a non-ischemic HF etiology.

Nonischemic Heart Disease With ALVD. No trial has specifically examined the effect of beta blockers on mortality in asymptomatic patients with reduced LVEF but no recent MI. Given the consistency of benefit observed with beta blockers across symptomatic populations, with and without ischemic heart disease, and in patients with prior MI, regardless of HF symptoms, it is reasonable to recommend use of these agents in asymptomatic patients with reduced LVEF in the absence of identifiable ischemic heart disease. See more about beta blockers in Section 7.

Aldosterone Antagonists in Patients With ALVD. Although aldosterone antagonists have been demonstrated to decrease morbidity and mortality in patients with moderate to severe symptoms of HF and reduced LVEF, there are currently no substantial data to suggest that these agents should be recommended as treatment for patients with ALVD. Studies are ongoing to determine the potential of aldosterone antagonists to impact the process of remodeling.

Device Therapies in Patients With ALVD

Cardiac resynchronization therapy (CRT) in patients with ALVD has not been investigated in a large clinical trial. Two trials, the Resynchronization Reverses Remodeling in systolic Left Ventricular Dysfunction (REVERSE)[30] and the Multicenter Automatic Defibrillator Implantation Trial with Cardiac Resynchronization Therapy (MADIT-CRT)[31] have studied CRT in patients with NYHA class I and II HF. Further research in a true ALVD population is needed to evaluate the efficacy of CRT in this setting.

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Section 6: Nonpharmacologic Management and Health Care Maintenance in Patients With Chronic Heart Failure

Overview

Nonpharmacologic management strategies represent an important contribution to heart failure (HF) therapy. They may significantly impact patient stability, functional capacity, mortality, and quality of life. Most of the recommendations that follow derive from consensus expert opinion or are based on theory extrapolated from limited trial data in the elderly or chronic disease populations.

Diet and Nutrition

Recommendations

6.1 Dietary instruction regarding sodium intake is recommended in all patients with HF. Patients with HF and diabetes, dyslipidemia, or severe obesity should be given specific dietary instructions. (Strength of Evidence = B)

6.2 Dietary sodium restriction (2-3 g daily) is recommended for patients with the clinical syndrome of HF and preserved *or* depressed left ventricular ejection fraction (LVEF). Further restriction (<2 g daily) may be considered in moderate to severe HF. (Strength of Evidence = C)

Background

Excessive dietary sodium intake is a common proximate cause of worsening symptoms and hospitalization for HF exacerbation.[1–3] Furthermore, dietary sodium restriction typically results in a decrease in the diuretic dose required for maintenance of a euvolemic state and clinical stability. This is important because loop diuretics increase plasma renin activity and may adversely impact clinical outcomes through neurohormonal stimulation.[4] Studies of sodium restriction indicate an impact on such parameters as quality of life and even functional status,[5] but not mortality. Despite limited clinical trial data, sodium restriction remains an important and common component of HF disease management programs.[6]

The ''average'' American diet contains between 8,000 and 10,000 mg sodium; certain ethnic diets are typically several-fold higher. (See Table 3.3 in Section 3 for salt-sodium equivalents.) A ''low-sodium'' or ''no added salt diet'' as defined by the American Heart Association is 4000 mg sodium. The current recommendation from the American Heart Association and the United States Department of Agriculture (USDA) for the general population is to limit sodium intake to 2300 mg per day, while the current USDA recommendation for those with hypertension, blacks and middle-aged and older people is 1500 mg per day for hypertension prevention.[7] Thus, although there remains no evidence about the ideal level of sodium restriction in patients with HF because of lack of studies on this topic, it is reasonable to recommend that sodium intake be limited to 2000−3000 mg per day.

Because following a low sodium diet is a specific activity, greater patient success can be expected when the clinician provides the patient with a daily sodium intake target and the knowledge and skills to reach that target. It is not enough to simply ask patients to follow a low salt diet. Nor is it sufficient to advise not salting food at the table or while cooking as most (~70%) of our daily sodium intake comes from processed and pre-packaged foods. Appropriate education and counseling regarding the 2000−3000 mg sodium diet recommendation is covered in Section 8.

Additional dietary instruction should be provided to all patients with HF who have comorbid conditions, including arteriosclerosis, diabetes, renal insufficiency, or obesity. Patients with hyperlipidemia or known underlying coronary or peripheral arteriosclerosis should be given specific instruction regarding dietary fat and cholesterol restriction according to national guidelines, such as the National Cholesterol Education Program. Diabetics exhibiting poor glycemic control or with significant albuminuria should receive individualized nutritional counseling regarding protein and carbohydrate consumption and caloric constraints as indicated to reduce risk for morbidity and mortality. Aggressive management of hyperglycemia diminishes osmotic forces leading to water retention and glomerular hyperfiltration, while reducing infection risk and the long-term risk of additional end-organ damage.[8] Patients with significant underlying renal insufficiency may require individualized instruction regarding protein, potassium, phosphorus, or other dietary constraints to preserve electrolyte and acid-base homeostasis.

Obesity is independently associated with HF and contributes to the development of additional HF risk factors, including hypertension, LV hypertrophy and diastolic filling abnormalities. Obesity is linked to insulin resistance and glucose intolerance, hyperaldosteronism, salt sensitivity, and plasma volume expansion, creating both pressure and volume overload stressors with increased systemic vascular resistance. The metabolic demand of excessive adipose tissue increases cardiac output requirements, making cardiomyopathy with HF the leading cause of death in patients with severe obesity. Arrhythmia risk is increased in association with prolongation of the QT interval frequently seen in the setting of morbid obesity. Sleep-disordered breathing is linked to pulmonary hypertension, right ventricular failure, and hypoxemia. For both obesity-cardiomyopathy and obesity-hypoventilation syndromes, weight loss and sodium restriction are effective measures to improve symptoms and prognosis.[9]

A number of recent studies evaluating the relationship between body mass index (BMI) and mortality have suggested that overweight (BMI 25−29.9 kg/m^2) and obese (BMI ≥30 kg/m^2) people with HF have a better survival

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than healthy weight people (BMI 18.5−24.9 kg/m^2) with HF.[10−13] Reasons for this ''obesity paradox'' remain unexplained. Low BMI (<18.5 kg/m^2) subjects with HF appear to have the highest mortality.[11−14] At least one study suggests that severely obese subjects (BMI ≥35 kg/m^2) also have a higher mortality than normal weight or mild to moderately obese people with HF, resulting in a ''J'' shaped curve for the BMI-mortality relationship.[14]

When risk of death was assessed in 359,387 people from the general population using BMI, waist circumference and waist-hip ratio, general and abdominal obesity were associated with risk of death.[15] In patients with HF, central adiposity, assessed by waist-hip ratio, but not BMI, was predictive of all-cause mortality independent of age and gender.[16] Of note, waist-hip ratio was more strongly associated with LV diastolic function as well. After adjustment for LVEF and diastolic function, waist-hip ratio was no longer a risk factor for mortality. Thus, ventricular dysfunction may be an important mediating factor between waist-hip ratio and mortality.[16] Another explanation for the ''obesity paradox'' may be that it is the change in weight over time, not the specific weight at any given time, that predicts mortality. Normal weight people with HF may have been overweight or obese and are actively losing weight.[11] It is also possible that HF is detected earlier in overweight and obese people due to symptom exacerbation caused by excess weight.[12] Other explanations include the use of higher doses of beneficial medications or the benefits of elevated TNF-α receptor levels in the obese.[17,18] Although it seems unlikely that there is a beneficial effect of obesity in people with HF, the explanation for the ''obesity paradox'' remains uncertain. Until further data are available, caloric restriction as part of the treatment of the severely obese patient with HF and weight stabilization or reduction in overweight and mildly obese patients seems reasonable.

There are defined risks of extreme calorie and carbohydrate restriction that may be increased in patients with HF. Electrolyte abnormalities and ketosis may occur with these diets and require frequent monitoring and physician oversight.

For HF patients with a BMI >35, gastrointestinal surgery is an option, with operative risk dependent on clinical symptoms, hemodynamic stability, and stability of coronary artery disease.[19] Surgical intervention is the only weight loss therapy with reasonable long-term result maintenance, although operative morbidity and mortality are substantial.[20] One recent study found that weight reduction after bariatric surgery in subjects with morbid obesity may reverse LV hypertrophy.[19] Preliminary data also suggest that in subjects with morbid obesity and reduced systolic function, bariatric surgery may lead to improvements in cardiac function.[21−23] It is therefore a consideration in morbidly obese patients for whom all other weight loss measures have failed.

Recommendation

6.3 Restriction of daily fluid intake to <2 L is recommended in patients with severe hyponatremia (serum sodium <130 mEq/L) and should be considered for all patients demonstrating fluid retention that is difficult to control despite high doses of diuretic and sodium restriction. (Strength of Evidence = C)

Background

Fluid restriction is indicated in the setting of symptomatic hyponatremia (serum sodium <130 mEq/L), whether or not it is precipitated by pharmacologic therapy. Concomitant dietary sodium restriction facilitates maximal diuresis and may reduce hospital length of stay. In the outpatient setting, fluid restriction generally is reserved for advanced HF refractory to high doses of oral diuretic agents. Fluid restriction in the outpatient setting has many inherent logistical difficulties, often leading to increased stress, anxiety, and poor adherence with therapy. Most disease management programs monitor patient volume status reliably and effectively through the attainment of daily morning weight, rather than through patient measurement of daily intake and output.[24]

Apparent diuretic refractoriness is most often a reflection of nonadherence with dietary sodium restriction or prescribed pharmacologic therapy, unrecognized drug interactions (eg, nonsteroidal anti-inflammatory agents [NSAIDs] and glitazones) or the uncommon patient with excessively high fluid intake (>6 L/day). Physiologic diuretic refractoriness can be observed with chronic loop diuretic administration, primarily from distal renal tubular hypertrophy that facilitates enhanced sodium reabsorption. On the other hand, ''true'' diuretic refractoriness may reflect underlying disease progression with reduced cardiac output and effective renal plasma flow, development of significant intrinsic renal insufficiency, or nephrosis.

Recommendation

6.4 It is recommended that specific attention be paid to nutritional management of patients with advanced HF and unintentional weight loss or muscle wasting (cardiac cachexia). Measurement of nitrogen balance, caloric intake, and prealbumin may be useful in determining appropriate nutritional supplementation. Caloric supplementation is recommended. Anabolic steroids are not recommended for cachexic patients. (Strength of Evidence = C)

Background

Cardiac cachexia is a well-described phenomenon that is associated with intense activation of the cytokine, tumor necrosis factor-α, or chronically low cardiac output states. Similar features are observed in patients with terminal cancer, acquired immunodeficiency syndrome (AIDS), and chronic inflammatory diseases. Such patients are at extremely high risk for serious morbidity, such as infection, hospitalization and impaired wound healing.

In HF patients with reduced LVEF, tumor necrosis factor-α, levels are highest in advanced disease and correlate with the highest risk of mortality. Formal metabolic evaluation and determination of minimal nutritional requirements should be strongly considered for patients demonstrating this muscle-wasting syndrome. Specific recommendations have been made for these patients, including altering the size and frequency of meals and ensuring a high-energy diet.[25]

There are no data to support the use of anabolic steroids or human growth hormone supplementation in patients with cardiac cachexia and skeletal muscle wasting. Initial enthusiasm for this approach was based on data suggesting that small doses of testosterone have a beneficial effect on dysfunctional myocardium.[26] However, long-term exposure to these compounds has been reported to increase ischemia risk and to promote adverse ventricular remodeling risk. Fluid retention and electrolyte abnormalities are frequently observed with the use of this therapy. Additional serious risks include increased thrombogenicity and erythrocytosis, as well as benign prostatic hypertrophy and prostate cancer.

Recommendation

6.5 Patients with HF, especially those on diuretic therapy and restricted diets, should be considered for daily multivitamin-mineral supplementation to ensure adequate intake of the recommended daily value of essential nutrients. Evaluation for specific vitamin or nutrient deficiencies is rarely necessary. (Strength of Evidence = C)

Background

Based on research, dietary guidelines for individuals at risk for developing HF are more established than for those who already have the condition.[27] Balanced nutrition with multivitamin/mineral supplementation to fulfill the recommended daily value of essential nutrients is prudent for persons with any chronic disease, including HF. Multivitamin/mineral supplementation may offset nutritional imbalances from early satiety and altered digestive efficiency related to decreased absorption, enhanced water-soluble vitamin and mineral loss from diuretic administration, and increased utilization due to oxidative stress.[28] It should also be recognized that population-related issues, such as old age or other chronic conditions, rather than HF itself, can be responsible for nutritional deficiencies in patients with HF.[29]

In general, for most patients with HF, a prudent diet providing adequate protein, carbohydrate, and calories according to age, gender, and activity level is advisable. Dietary supplementation consisting of a daily multiple-vitamin should be considered, given that most American diets are inadequate in providing the recommended basic nutrient requirements.

Studies estimate that approximately 50% of patients with HF consume herbal, megavitamin, or other dietary supplements.[30] The likelihood of an adverse reaction or vitamin toxicity increases with consumption of multiple supplements, the safety and efficacy of which are not well documented. It is therefore important to ask patients with HF about supplements they are already taking before recommending a daily multiple vitamin.

Recommendation

6.6 Documentation of the type and dose of naturoceutical products used by patients with HF is recommended. (Strength of Evidence = C)

Naturoceutical use is not recommended for relief of symptomatic HF or for the secondary prevention of cardiovascular events. Patients should be instructed to avoid using natural or synthetic products containing ephedra (ma huang), ephedrine, or its metabolites because of an increased risk of mortality and morbidity. Products should be avoided that may have significant drug interactions with digoxin, vasodilators, beta blockers, antiarrhythmic drugs, and anticoagulants. (Strength of Evidence = B)

Background

Naturoceutical use cannot be recommended for the relief of HF symptoms or for the secondary prevention of cardiovascular events. Given the paucity of efficacy data about naturoceutical products, reporting suspected adverse effects or drug interactions to the Food and Drug Administration is strongly encouraged.

There are several agents with documented potential to do harm. Natural or synthetic catecholamine-like products containing ephedra (ma huang), ephedrine metabolites, or imported Chinese herbs are specifically contraindicated in HF. Hawthorne (Cratageus) products appear to have inodilator activity, increasing the risk of orthostatic hypotension and possibly arrhythmia. Hawthorne potentiates the action of vasodilator medications and increases serum digoxin levels. One recent long-term placebo-controlled trial failed to show any incremental benefit when hawthorn extract was given with standard drug therapy to patients with chronic HF. It did show, however, that the drug appeared safe to use with angiotensin converting enzyme (ACE) inhibitors, beta blockers, and other standard HF medications.[31] Many other naturoceutical products, including garlic, gingko biloba, and ginseng, have antiplatelet effects or potential anticoagulant interactions.[32]

Other Therapies

Recommendation

6.7 Continuous positive airway pressure to improve daily functional capacity and quality of life is recommended in patients with HF and obstructive sleep apnea documented by approved methods of polysomnography. (Strength of Evidence = B)

Background

Sleep-disordered breathing is highly prevalent in HF patients.[33–35] Formal sleep evaluation is therefore recommended for patients who remain symptomatic despite

optimal HF therapy. Testing should be considered for patients with a positive screening questionnaire or whose sleep partner reports signs suggesting apnea or periodic breathing. Whether clinical outcome is favorably affected by treatment of sleep-disordered breathing is unclear, but patient quality of life and functional capacity is increased by treatment when the respiratory disturbance index is at least moderately elevated, and individual studies have shown that use of continuous positive airway pressure (CPAP) reduces edema, daytime muscle sympathetic nerve activity, systolic blood pressure, frequency of ventricular premature beats during sleep, and improves LV function.[36–40] Concomitant treatment for restless leg syndrome may be reduced when the patient is treated for associated sleep-disordered breathing.

The other component of sleep-disordered breathing, central sleep apnea, was studied in a large-scale trial that tested the hypothesis that CPAP would improve the survival rate without transplantation for patients with central sleep apnea and HF. The Canadian Continuous Positive Airway Pressure for Patients with Central Sleep Apnea and Heart Failure trial (CANPAP) of 258 patients found that those patients randomized to CPAP had attenuated central sleep apnea, improved nocturnal oxygenation, increased LVEF, and improved 6-minute walk distances, but did not survive longer.[41]

Recommendation

6.8 Supplemental oxygen, either at night or during exertion, is not recommended for patients with HF in the absence of an indication of underlying pulmonary disease. Patients with resting hypoxemia or oxygen desaturation during exercise should be evaluated for residual fluid overload or concomitant pulmonary disease. (Strength of Evidence = B)

Background

Pulmonary vascular congestion creating resting or exertional hypoxemia requires aggressive diuretic therapy, rather than supplemental oxygen. Oxygen supplementation is a useful therapeutic adjunct in hospitalized patients during acute decompensation or with coronary ischemia. Patients with residual resting hypoxemia or exertional arterial oxygen desaturation after optimization of intravascular volume should be evaluated for concomitant pulmonary disease, pleural effusion, pulmonary emboli, pulmonary hypertension, silent myocardial ischemia, obesity-hypoventilation syndrome, and sleep-disordered breathing.

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Recommendation

6.9 The identification of treatable conditions, such as sleep-disordered breathing, urologic abnormalities, restless leg syndrome, and depression should be considered in patients with HF and chronic insomnia. Pharmacologic aids to sleep induction may be necessary. Agents that do not risk physical dependence are preferred. (Strength of Evidence = C)

Background

Chronic insomnia is associated with a risk of psychological instability and impaired cognitive function. After metabolic, physiologic, pharmacologic, and dietary causes are excluded, screening should be considered for urologic abnormality, sleep-disordered breathing, restless leg syndrome, depression, and anxiety disorders. Nocturnal anxiety may be a manifestation of paroxysmal nocturnal dyspnea. Sedatives can worsen apnea and should be initially eliminated. Paradoxical agitation from the use of antihistamine products or benzodiazepine preparations is not uncommon. For these reasons, the use of medication to aid sleep induction should be undertaken only when necessary, and then with caution and careful monitoring.

Specific Activity and Lifestyle Issues

HF is a syndrome with an enormous impact on the quality of life of patients and families. HF can affect employment, relationships, leisure activities, eating, sleeping, and sexual activity-to name just a few critical areas. Physicians have a significant opportunity to improve their patients' quality of life by initiating discussion regarding these issues and providing education, feedback, and support.

Recommendation

6.10 It is recommended that screening for endogenous or prolonged reactive depression in patients with HF be conducted following diagnosis and at periodic intervals as clinically indicated. For pharmacologic treatment, selective serotonin reuptake inhibitors are preferred over tricyclic antidepressants, because the latter have the potential to cause ventricular arrhythmias, but the potential for drug interactions should be considered. (Strength of Evidence = B)

Background

Depression is common in both elderly and HF populations and has an enormous impact on quality of life and functional capacity.[42–44] It is an independent risk factor for coronary heart disease and is associated with increased morbidity and mortality.[43,45] In a recent prospective cohort

study in outpatients with HF and LVEF <40%, living alone, alcohol abuse, perception of medical care as being a substantial economic burden, and health status were independent predictors of developing depressive symptoms.[46] Clinicians should be aware of patients at risk for the development of depression so that they may be targeted for screening and psychosocial intervention, as needed. Several screening questionnaires for depression are available.

Selective serotonin reuptake inhibitors (SSRI) are effective and generally safe in patients with HF. Tricyclic antidepressants have anticholinergic that increase heart rate, promote orthostatic hypotension, and alter ventricular repolarization. A recent study evaluating the association of long-term mortality with antidepressant use versus depression in patients with HF found that depression, but not the use of an SSRI, was associated with a 33% increased mortality risk in 1006 patients followed up over a mean of 972 days (HR 1.33, 95% CI 1.07−1.66).[47]

Recommendation

6.11 Nonpharmacologic techniques for stress reduction may be considered as a useful adjunct for reducing anxiety in patients with HF. (Strength of Evidence = C)

Background

Anxiety is commonly associated with depression, and often manifests as the inability to adjust to stressful situations. Although it is depression that is predictive of a worse prognosis,[48] anxiety should be taken seriously and reduced as much as possible. An assessment of intrinsic coping skills may be useful. Relaxation techniques such as meditation and biofeedback may improve patient daily functioning.[49] In one small study, researchers found that acupuncture inhibited sympathetic activation during mental stress in patients with advanced HF.[50]

Effective communication skills can reduce anxiety. The diagnosis of HF and its prognosis are likely to provoke anxiety. Anxiety, in turn, may contribute to a patient's inability to comprehend or follow a treatment plan. In discussing recommendations regarding end-of-life issues, including advance directives, care should be taken to avoid inducing excessive anxiety.

Recommendation

6.12 It is recommended that treatment options for sexual dysfunction be discussed openly with both male and female patients with HF. (Strength of Evidence = C)

The use of phosphodiesterase-5 inhibitors such as sildenafil may be considered for use for sexual dysfunction in patients with chronic stable HF. These agents are not recommended in patients taking nitrate preparations. (Strength of Evidence = C)

Background

Sexual dysfunction is common in patients with heart disease and should be discussed openly with all patients, male and female. Standard HF therapy may worsen sexual dysfunction in some patients, leading to nonadherence and worsening of HF symptoms.[51] Use of phosphodiesterase-5 inhibitors generally is safe when HF symptoms are compensated and there is no concomitant use of nitrate medications. In fact, a number of studies showed a positive impact of sildenafil on cardiac performance, particularly exercise capacity, in patients with HF.[52−54]

Many other nonpharmacologic aids exist for erectile dysfunction, impotence, and other forms of sexual dysfunction. Patients reluctant to initiate discussion regarding sexuality or who are unaware of treatment options may be intentionally noncompliant with HF medications to determine their influence on sexual dysfunction. A proactive discussion may therefore alleviate some risk of adherence-related clinical instability.

Health Care Maintenance Issues

Routine health care maintenance is often neglected by patients with HF, who are consumed with cardiovascular issues. Access to care may be an additional problem among the elderly and those with limited socioeconomic means. General health measures are at least as important in patients with HF as they are in other populations.

Recommendation

6.13 It is recommended that patients with HF be advised to stop smoking and to limit alcohol consumption to ≤2 standard drinks per day in men or ≤1 standard drink per day in women. Patients suspected of having an alcohol-induced cardiomyopathy should be advised to abstain from alcohol consumption. Patients suspected of using illicit drugs should be counseled to discontinue such use. (Strength of Evidence = B).

Background

All patients with the clinical syndrome of HF who abuse tobacco, alcohol, or illicit drugs should be counseled to stop. For such patients, these recommendations carry even greater potential benefit than they do in the general population.[55] Nicotine has vasoconstrictor activity, which can worsen hemodynamics and antagonize vasodilator effect. Transdermal nicotine preparations do not appear to significantly increase cardiovascular risk, even in high-risk patients, although physician-monitored use is advisable. Additional pharmacologic aids for tobacco withdrawal, such as bupropion, have not been associated with exacerbation of HF.

Alcohol-induced dilated cardiomyopathy is generally associated with chronic daily consumption of at least 70 g of

ethanol. Alcohol alters myocardial metabolism in many ways, significantly affecting fatty acid composition of the sarcolemma. Confounding nutritional and vitamin deficiencies coexist in chronic alcoholism and may adversely affect ventricular function. Renal magnesium and potassium wasting are enhanced. In the Studies of Left Ventricular Dysfunction (SOLVD) trials, a positive relationship was found between light to moderate alcohol intake and significant increases in serum markers of inflammation, shown to correlate with adverse clinical outcome.

The potential for reversal of ventricular remodeling and normalization of LVEF with cessation of alcohol ingestion are well recognized and correlate with improved prognosis. For patients who are not suspected of having an alcohol-induced cardiomyopathy, there is controversy regarding the impact of small amounts of alcohol. Light to moderate alcohol consumption (1−2 drinks per day) does not appear to alter the risk for HF in patients with LV dysfunction after myocardial infarction or to alter outcomes in patients with HF.[56,57]

Recommendations

6.14 Pneumococcal vaccine and annual influenza vaccination are recommended in all patients with HF in the absence of known contraindications. (Strength of Evidence = B)

6.15 Endocarditis prophylaxis is not recommended based on the diagnosis of HF alone. Consistent with the AHA recommendation, 'prophylaxis should be given for only specific cardiac conditions, associated with the highest risk of adverse outcome from endocarditis.' [58] These conditions include: 'prosthetic cardiac valves; previous infective endocarditis; congenital heart disease (CHD)' such as: unrepaired cyanotic CHD, including palliative shunts and conduits; completely repaired congenital heart defect with prosthetic material or device, whether placed by surgery or by catheter intervention, during the first six months after the procedure; repaired CHD with residual defects at the site or adjacent to the site of a prosthetic patch or prosthetic device (which inhibit endothelialization) cardiac transplantation recipients who develop cardiac valvulopathy. (Strength of Evidence = C)

Background

Pulmonary congestion and pulmonary hypertension increase the risk of lung infection. Therefore, administration of pneumococcal vaccine and annual influenza vaccines is highly recommended in HF patients, as is counseling patients to seek early evaluation for potentially serious infections. Additional vaccines, such as hepatitis and specific immunization matching foreign travel standards, should be given if appropriate. Maintenance of tetanus toxoid vaccination is prudent in all patients with HF.

There are few indications for infective endocarditis (IE) prophylaxis because the risk of IE due to dental or other procedures is quite low compared to the prevalence of bacteremia due to activities of daily living, such as chewing and teeth brushing.[58] Prophylaxis should follow American Heart Association/American College of Cardiology (AHA/ACC) guidelines in the setting of valvular heart disease when applicable. [58] Whether functional mitral regurgitation resulting from LV chamber and valve ring dilation carries the same attributable risk as that of primary valvular disorders is unclear from available data, although most experts would recommend treatment. When a patient has an implanted intravascular device, such as a pacemaker or automated internal cardiac defibrillator, most electrophysiologists recommend antibiotic prophylaxis under the same conditions as valvular heart disease, at least for the first 3 months after implantation.

Recommendation

6.16 Nonsteroidal anti-inflammatory drugs, including cyclooxygenase-2 inhibitors, are not recommended in patients with chronic HF. The risk of renal failure and fluid retention is markedly increased in the setting of reduced renal function or ACE-inhibitor therapy. (Strength of Evidence = B)

Background

The need for analgesic medication for musculoskeletal complaints is common in HF patients, partially because HF is predominantly a disease of the elderly.[59] Unsuspected use of NSAID products may explain worsening renal function, hyperkalemia, fluid retention, or hypertension among HF patients. NSAID use has been implicated in the onset of HF symptoms in the elderly, perhaps unmasking underlying ventricular dysfunction.[60] The use of cyclooxygenagase-2 inhibitors has been associated with a higher risk of hospitalization for HF, although some studies indicate that celecoxib appears safer than rofecoxib.[61,62] All patients should be instructed to avoid the use of these products, unless all other treatment modalities have been exhausted. When these agents are prescribed, there should be careful clinical monitoring and laboratory assessment of renal function.

The risk of gout is increased in HF patients. Diuretic use, obesity, renal impairment, and alcohol consumption are additional risk factors. Colchicine and corticosteroids are preferred to NSAIDs as initial therapy for acute attacks.

Recommendations

6.17 It is recommended that patients with new- or recent-onset HF be assessed for employability following a reasonable period of clinical stabilization. An objective assessment of functional exercise capacity is useful in this determination. (Strength of Evidence = B)

6.18 It is recommended that patients with chronic HF who are employed and whose job description is compatible with their prescribed activity level be encouraged to remain employed, even if a temporary reduction in hours worked or task performed is required. Retraining should be considered and supported for patients with a job demanding a level of physical exertion exceeding recommended levels. (Strength of Evidence = B)

Exercise Rehabilitation as Therapy for HF

Recommendation

6.19 It is recommended that patients with HF undergo exercise testing to determine suitability for exercise training (patient does not develop significant ischemia or arrhythmias). (Strength of Evidence = B)

If deemed safe, exercise training should be considered for patients with HF in order to facilitate understanding of exercise expectations (heart rate ranges and appropriate levels of exercise training), to increase exercise duration and intensity in a supervised setting, and to promote adherence to a general exercise goal of 30 minutes of moderate activity/exercise, 5 days per week with warm up and cool down exercises. (Strength of Evidence = B)

Background

Cardiac/exercise rehabilitation offers a potential therapeutic approach in the management of patients with HF. The HF-ACTION trial (A Controlled Trial Investigating Outcomes of Exercise Training), a large, multicenter, randomized controlled study, failed to show significant improvement in all-cause mortality or all-cause hospitalization in patients who received a 12-week (3 times/week) exercise training program followed by 25−30 minute, 5 days/week home-based, self-monitored exercise workouts on a treadmill or stationary bicycle.[63] However, after controlling for HF etiology, atrial fibrillation, exercise duration and depression, patients who exercised had an 11% risk reduction in the primary endpoint ($P=0.03$). Additionally, cardiovascular mortality or HF hospitalization was reduced by 15% after adjustment ($P=0.03$), and at three months after enrolment, quality of life was significantly improved in the exercise group.[64] In HF-ACTION, exercise was safe and may be effective in improving clinical outcomes in patients not at highest prognostic risk. Additionally, functional status was significantly improved in patients receiving usual care plus exercise training in HF-ACTION. Distance walked at 3 months was higher and cardiopulmonary exercise time and peak oxygen consumption were improved at both 3 and 12 months in the exercise training group.[63]

HF-ACTION investigators found that many participants were non-adherent to the prescribed exercise program. In the first three months after enrolment, about 40% of patients fully adhered to the exercise duration goal and an additional 15% partially adhered, but in the last year of enrollment, less than 30% of participants were fully adherent and overall adherence had dropped below 45%.[65] In a sub-analysis of HF-ACTION, researchers found that participants in the exercise training group with a higher volume of exercise per week had a reduction in all cause death or hospitalization, cardiovascular death or cardiovascular hospitalization and cardiovascular death or HF hospitalization at 90 days. Moreover, peak oxygen consumption, six-minute walk distance and quality of life all significantly improved in participants who exercised at a higher volume.[65] HF-ACTION results provide further evidence beyond the many single center, short-term studies that showed that supervised exercise training improved quality of life and exercise capacity in patients with HF.[66−78]

Exercise training was found to have physiological benefits in patients with HF. Exercise training improved autonomic dysfunction and heart rate variability and was associated with a fall in resting plasma norepinephrine levels.[67,79−82] It was found to improve exercise cardiac output, decrease peripheral vascular tolerance, and produce favorable changes in skeletal muscle metabolism and structure.[83,84] Exercise training has been demonstrated to improve endothelium-dependent vasodilatation and coronary blood flow reserve in epicardial coronary vessels of patients with coronary artery disease, which may account for the observation that exercise training improves myocardial perfusion without reducing coronary obstruction or enhancement of collateral blood flow.[85−89] Despite the favorable mechanistic studies, HF-ACTION is the only definitive study conducted to test whether exercise training for patients with HF can improve survival or reduce risk of hospitalization. The available trial data, from studies underpowered to provide definitive results had mixed results.[89,90]

Exercise Intolerance in HF. Exercise intolerance is an important adverse effect of HF and contributes significantly to the poor quality of life experienced by patients suffering from this syndrome. Impaired exercise capacity is an independent predictor of survival, and progressive loss of functional capacity is characteristic as HF worsens clinically.[91−94] Intense investigation has focused for the past 2 decades on the potential mechanisms responsible for exercise intolerance in patients with HF. Interestingly, the degree of LV systolic dysfunction has been found to be poorly correlated with the degree of exercise intolerance.[95−97] In contrast, the importance of reduced blood flow to exercising muscle is apparent from the closer relationship between exercise capacity and exercise cardiac output.[98−111]

Summary. Clinical studies support the concept that exercise training is safe and may be beneficial in patients with HF from LV systolic dysfunction. Evidence for benefit is derived both from mechanistic studies, short-term clinical

trials that show physiologic improvement and benefits on exercise capacity following exercise training, and a large, multicenter study of long term benefits.[63,64,112] The possibility exists that exercise training could be harmful to patients with HF, especially if it is applied in a population not consistent with those participating in completed studies. At present, exercise training cannot be recommended in patients with LV systolic dysfunction who had a major cardiovascular event or procedure within the last six weeks, in patients receiving cardiac devices that limit the ability to achieve target heart rates, and in patients with significant arrhythmia or ischemia during baseline cardiopulmonary exercise testing.

Potential Pathophysiologic Role of Hemoglobin in HF: An Unresolved Issue

Anemia and reduced hemoglobin have been associated with HF for decades. Until recently the assumption was that the observed reduction in hemoglobin was consistent with ''anemia of chronic disease,'' was not of prognostic significance and did not need to be treated. A number of recent studies demonstrated a significant association between reduced hemoglobin and a number of adverse outcomes, including exercise capacity, quality of life, and risk of death or hospitalization.

Prevalence and Pathogenesis. The prevalence of reduced hemoglobin and anemia in HF varies widely. Depending on the anemia criterion used and patient population studied, from 10% to 70% of HF patients meet criteria for anemia.[113] Reduced renal function is increasingly common in patients with HF and is a well-documented cause of anemia.[114] Anemia is common in elderly patients with HF, especially those with a history of hospitalization for HF, and patients with advanced clinical class are more likely to have reduced hemoglobin. A prospective ongoing study of patients with HF seen in specialty clinics and community cardiology practices suggests approximately 30 percent of patients with HF are anemic.[115,116]

The pathogenesis of anemia in patients with HF is uncertain. Several potential mechanisms have been proposed, including impaired renal function, malabsorption, nutritional deficiency and cytokine activation.[114,117–120]

Morbidity and Mortality. Preliminary analysis of the results of prospective quality of life measurements in unselected outpatients with HF seen in specialty clinics or community cardiology practices suggests that reduced hemoglobin is associated with poorer quality of life.[121] Reduced hemoglobin has been shown to be a risk factor for hospitalization for HF. A retrospective study of Medicare patients reviewed the association between outcome and hemoglobin in 665 patients admitted to community hospitals for HF.[122] The risk of hospitalization was significantly increased in patients who also had anemia and was nearly doubled among those patients with anemia and chronic kidney disease (defined as a serum creatinine >1.4 mg/dL for women and >1.5 mg/dL for men).

A number of retrospective database studies have demonstrated that reduced hemoglobin is significantly associated with increased mortality in patients with HF.[123–125] Early work in a high-risk subset of patients with HF suggests that dilutional anemia, even more than true anemia, is associated with a poor prognosis. Hemodilution can worsen HF by impairing peripheral oxygen delivery, and the volume overload that occurs with hemodilution increases pulmonary capillary wedge pressure. As a result, survival in patients with HF and dilutional anemia is decreased compared with that of patients with HF and true anemia.[126]

Therapeutic Experience. There are very preliminary data to suggest that increasing hemoglobin may have beneficial effects in patients with HF. A recent single-center, small-scale randomized, single-blind, placebo-controlled study evaluated the effect of 3 months of erythropoietin treatment on exercise capacity in 26 patients with anemia and New York Heart Association (NYHA) class III-IV HF.[127] Significant improvement in peak oxygen consumption (VO_2 max) occurred with erythropoietin treatment versus no significant change in the control patients. In the and Ferinject Assessment in Patients with Iron Deficiency and Chronic Heart Failure (FAIR-HF) trial, 200 mg of intravenous iron improved symptoms, functional capacity, and quality of life in patients with chronic heart failure, reduced LVEF, and iron deficiency.[128]

Possible Adverse Effects. Although the association studies and the preliminary clinical investigations suggest potential benefit from augmenting hemoglobin in patients with HF, there are theoretical concerns about this form of therapy. Erythropoietin therapy has been associated with worsening hypertension in 20% to 30% of patients on hemodialysis.[129] Raising the hemoglobin level could adversely affect viscosity, which could lead to increased risk of thrombosis. Increased risk of thrombosis also could occur as a result of increased platelet activation, increased blood viscosity, or effects on the levels of proteins C and S.[130–135]

Summary. Retrospective analysis of database and early interventional studies raises the possibility that augmenting hemoglobin concentration may benefit patients with HF. However, given the risk carried by higher hemoglobin levels, more definitive data on the clinical benefits of anemia therapy in HF are needed. Several important questions remain unanswered concerning the ideal implementation of this therapy, including the optimal hemoglobin level and the appropriate rate of rise of hemoglobin when therapy is initiated. Randomized placebo controlled trials in patients with HF, including Reduction of Events with Darbepoetin alfa in Heart Failure (RED-HF), and IRON-HF are underway to establish the safety and efficacy of this and other treatment strategies.

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Section 7: Heart Failure in Patients With Reduced Ejection Fraction

Overview

There are 3 primary issues that must be considered when treating heart failure (HF) patients with reduced left ventricular ejection fraction (LVEF): (1) improving symptoms and quality of life, (2) slowing the progression or reversing cardiac and peripheral dysfunction, and (3) reducing mortality. General measures, such as salt restriction, weight loss, lipid control, and other nonpharmacologic measures are addressed in Section 6. Pharmacologic approaches to symptom control, including diuretics, vasodilators, intravenous inotropic drugs, anticoagulants, and antiplatelet agents are discussed at the end of this section.

Two classes of agents have become the recommended cornerstone of therapy to delay or halt progression of cardiac dysfunction and improve mortality: angiotensin-converting enzyme (ACE) inhibitors and beta blockers. Even while these agents are underused in the treatment of HF, new classes of agents have been added that show an impact on mortality, complicating decisions about optimal pharmacologic therapy. These include angiotensin receptor blockers (ARBs), aldosterone antagonists, and the combination of hydralazine and an oral nitrate, all of which are considered in the following recommendations.

ACE Inhibitors

Recommendation

7.1 ACE inhibitors are recommended for routine administration to symptomatic and asymptomatic patients with LVEF ≤ 40%. (Strength of Evidence = A)

ACE inhibitors should be titrated to doses used in clinical trials, as tolerated during concomitant uptitration of beta blockers. (Strength of Evidence = C).

Background

There is compelling evidence that ACE inhibitors should be used to inhibit the renin-angiotensin-aldosterone system (RAAS) in all HF patients with reduced LVEF, whether or not they are symptomatic (Table 7.1). A number of large clinical trials have demonstrated improvement in morbidity and mortality in HF patients with reduced LVEF, both chronically and post-myocardial infarction (MI).[1–3] The mortality benefit is strongest across New York Heart Association (NYHA) class II-IV HF, but appears present in patients who are NYHA class I as well.[4]

The major side effects of ACE inhibitors in patients with HF are hypotension and azotemia. Both are usually well tolerated and do not indicate the need to lower the dose or discontinue the ACE inhibitor. The azotemia commonly is related to a relative volume-depleted state caused by diuretic therapy and may be improved by a reduction in diuretic dose. Moderate renal insufficiency should not be considered a contraindication to the use of ACE-inhibitors, although careful attention to serum potassium and creatinine levels is imperative.[5] The major symptomatic side effect is a dry cough that usually does not require discontinuation of the drug. Care should be taken to distinguish between a cough that is ACE inhibitor-related and one that is due to worsening pulmonary congestion. If the cough impairs the patient's quality of life, alternative therapy, such as an ARB, is recommended.[6]

Recommendations

7.2 It is recommended that other therapy be substituted for ACE inhibitors in the following circumstances:

- **In patients who cannot tolerate ACE inhibitors due to cough, ARBs are recommended. (Strength of Evidence = A)**
- **The combination of hydralazine and an oral nitrate may be considered in such patients not tolerating ARB therapy. (Strength of Evidence = C)**
- **Patients intolerant to ACE inhibitors from hyperkalemia or renal insufficiency are likely to experience the same side effects with ARBs. In these cases, the combination of hydralazine and an oral nitrate should be considered. (Strength of Evidence = C)**

7.3 ARBs are recommended for routine administration to symptomatic and asymptomatic patients with an LVEF ≤ 40% who are intolerant to ACE inhibitors for reasons other than hyperkalemia or renal insufficiency. (Strength of Evidence = A)

7.4 ARBs should be considered in patients experiencing angioedema while on ACE inhibitors based on their underlying risk and with recognition that angioedema has been reported infrequently with ARBs. (Strength of Evidence = B)

The combination of hydralazine and oral nitrates may be considered in this setting in patients who do not tolerate ARB therapy. (Strength of Evidence = C)

Background

Both ACE inhibitors and ARBs inhibit the RAAS, but by different mechanisms. ACE inhibitors block an enzyme responsible for converting angiotensin I to angiotensin II and for degrading various kinins. However, during chronic therapy, angiotensin II levels are not completely suppressed by ACE inhibitors for at least 2 reasons. Instituting an ACE inhibitor increases renin levels, resulting in higher levels of angiotensin I, which will tend by mass action to produce greater angiotensin II levels. Production of angiotensin II may also occur through non-ACE enzyme systems not blocked by

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Table 7.1. ACE-inhibitor, Angiotensin Receptor Blocker, and Beta-Blocker Therapy in HF with Low LVEF

Generic Name	Trade Name	Initial Daily Dose	Target Dose	Mean Dose Achieved in Clinical Trials
ACE-inhibitors				
Captopril	Capoten	6.25 mg tid	50 mg tid	122.7 mg/day[171]
Enalapril	Vasotec	2.5 mg bid	10 mg bid	16.6 mg/day[3]
Fosinopril	Monopril	5-10 mg qd	80 mg qd	n/a
Lisinopril	Zestril, Prinivil	2.5-5 mg qd	20 mg qd	*4.5 mg/day (low dose ATLAS) 33.2 mg/day (high dose ATLAS)[172]
Quinapril	Accupril	5 mg bid	80 mg qd	n/a
Ramipril	Altace	1.25-2.5 mg qd	10 mg qd	n/a
Trandolapril	Mavik	1 mg qd	4 mg qd	n/a
Angiotensin Receptor Blockers				
Candesartan	Atacand	4-8 mg qd	32 mg qd	24 mg/day[173]
Losartan	Cozaar	12.5-25 mg qd	150 mg qd	129 mg/day[174]
Valsartan	Diovan	40 mg bid	160 mg bid	254 mg/day[15]
Beta-blockers				
Bisoprolol	Zebeta	1.25 mg qd	10 mg qd	8.6 mg/day[24]
Carvedilol	Coreg	3.125 mg bid	25 mg bid	37 mg/day[43]
Carvedilol	Coreg CR	10 mg qd	80 mg qd	
Metoprolol succinate CR/XL	Toprol XL	12.5-25 mg qd	200 mg qd	159 mg/day[25]
Aldosterone Antagonists				
Spironolactone	Aldactone	12.5 to 25 mg qd	25 mg qd	26 mg/day[68]
Eplerenone	Inspra	25 mg qd	50 mg qd	42.6 mg/day[69]
Other Vasodilators				
Fixed dose Hydralazine/ Isosorbide dinitrate	BiDil	37.5 mg hydralazine/20 mg isosorbide dinitrate tid	75 mg hydralazine/40 mg isosorbide dinitrate tid	142.5 mg hydralazine/76 mg isosorbide dinitrate/day[81]
Hydralazine	Apresoline	37.5 mg qid	75 mg qid	270 mg/day[79]
Isosorbide dinitrate	Isordil	20 mg qid	40 mg qid	136 mg/day[79]

*No difference in mortality between high and low dose groups, but 12% lower risk of death or hospitalization in high dose group vs. low dose group.

inhibitors of this enzyme.[7,8] Thus, despite treatment with ACE inhibitors in patients with chronic HF, angiotensin II levels may remain elevated and increase over time.[9,10]

ARBs block the effects of angiotensin II on the ATI receptor, independent of the source of angiotensin II production. Coupled with angiotensin II "escape," this led to the hypothesis that ARBs might be superior to ACE inhibitors in HF and that the addition of ARBs to ACE inhibitors in patients with chronic HF might provide additional blockade of the RAAS and greater therapeutic benefit. ACE inhibitors reduce the degradation of kinins, which may lead to important therapeutic benefits not provided by ARBs, making the potential combination of the two agents more attractive.[11,12] Recommendations 7.13, 7.21, and 7.22 and the accompanying background discusses combination ACE-inhibitor and ARB therapy.

ACE inhibitors can have some troublesome side effects, including cough and angioedema, which may limit therapy with these agents. ARBs have been demonstrated to be well tolerated in randomized trials of patients judged to be intolerant of ACE inhibitors.[13,14] Both drugs have similar effects on blood pressure, renal function, and potassium.[13] The Candesartan in Heart Failure: Assessment of Reduction in Mortality and Morbidity (CHARM) Alternative trial prospectively tested the effect of an ARB in an ACE inhibitor intolerant population of patients with chronic HF and an LVEF $<40\%$. The addition of candesartan in these patients resulted in a reduction in the composite endpoint of cardiovascular death or hospital admission for HF from 40% in the control group to 33% in the candesartan group over a mean follow-up of 34 months with a trend toward decreased all-cause mortality.[13] Post-hoc subgroup analysis of a small number of patients in the Valsartan in Heart Failure Trial (Val-HeFT) also found that patients intolerant to ACE inhibitors had fewer HF hospitalizations and a trend toward improved mortality with the addition of valsartan.[15] These data suggest that an ARB should be used in ACE inhibitor intolerant patients with chronic HF and LVEF $<40\%$. ARBs should be titrated as tolerated, in conjunction with beta blocker therapy, to target doses used in clinical trials (Table 7.1). ARBs should be considered instead of ACE inhibitors primarily in patients who are intolerant of ACE inhibitors because of intractable cough or angioedema. ARBs appear as likely as ACE inhibitors to produce hypotension, worsening renal function, and hyperkalemia. See background to Recommendations 7.19–7.20 for information about isosorbide dinitrate/hydralazine as an alternative to ACE-inhibitor therapy in intolerant patients.

Angioedema and ARBs. Nearly three-quarters of patients in CHARM-Alternative were intolerant to ACE inhibitors primarily because of cough, but intolerance was also reported in 13% from symptomatic hypotension, 12% from renal dysfunction, and 4% from angioedema/anaphylaxis.[13] In that study, 3 patients taking candesartan and none taking placebo had angioedema. None of the episodes were life-threatening and only 1 of the 3 patients discontinued candesartan. The 3 cases of angioedema all occurred in the 39 patients intolerant to ACE inhibitors because of angioedema. Thus, the risk of recurrent angioedema with ARBs in patients with angioedema

from ACE inhibition appears to be acceptable, assuming careful instructions and patient monitoring.

Recommendation

7.5 Individual ARBs may be considered as initial therapy rather than ACE inhibitors for patients with the following conditions:
- **HF Post-MI (Strength of Evidence = A)**
- **Chronic HF and reduced LVEF (Strength of Evidence = B)**

Background

Support for the use of the ARB, valsartan, in patients post-MI is provided by The Valsartan in Acute Myocardial Infarction Trial (VALIANT), which randomized 14,703 patients 0.5 to 10 days post-MI to valsartan, valsartan plus captopril, or captopril alone. Patients enrolled had clinical or radiologic signs of HF, evidence of reduced LVEF, or both.[16] The primary end point was all-cause mortality. There were no statistical differences among the 3 groups at a mean follow-up of 24.7 months. With monotherapy, hypotension and renal dysfunction were more common in the valsartan group, and cough, rash, and taste disturbance were more common in the captopril group. The authors concluded that monotherapy with valsartan was equivalent to monotherapy with captopril. The Optimal Trial in Myocardial Infarction with the Angiotensin II Antagonist Losartan (OPTIMAAL) study randomized 5477 patient with HF or reduced LVEF post-MI to captopril or losartan.[17] The primary endpoint was all-cause mortality. There were 946 deaths during a mean follow-up of 2.7 years: 499 (18%) in the losartan group and 447 (16%) in the captopril group (relative risk 1.13 [95% CI 0.99−1.28], $P = .07$). Thus valsartan appears equivalent to captopril in patients with HF or reduced LVEF post-MI, but the data do not clearly support equivalence of losartan to captopril in these patients.

In patients with chronic HF and reduced LVEF, 2 reviews have addressed the equivalence of ARBs and ACE inhibitors.[18,19] One meta-analysis concluded that ARBs should be considered ''suitable alternatives'' to ACE inhibitors. The Centers for Medicare and Medicaid Services has used this review to consider both ARBs and ACE inhibitors as acceptable to satisfy performance standards in patients with HF.[20] A second review suggested that ACE-inhibitors remain first line therapy, whereas ARBs were recommended for ACE-intolerant patients.[18]

Beta Adrenergic Receptor Blockers (Table 7.1)

Recommendation

7.6 Beta blockers shown to be effective in clinical trials of patients with HF are recommended for patients with an LVEF ≤ 40%. (Strength of Evidence = A)

Background

Beta blocker therapy, advocated for HF by some investigators since the 1970s,[21] remains a major advance in the treatment of patients with HF and reduced LVEF. Several large-scale clinical trials, involving more than 10,000 patients, have provided unequivocal evidence of important reductions in both mortality and morbidity.[22−28] The marked beneficial effects of beta blockade has been well demonstrated in large-scale clinical trials of symptomatic patients with NYHA class II-IV HF and reduced LVEF using carvedilol, bisoprolol, and metoprolol controlled release/extended release (CR/XL) (Table 7.1).[24−28] These trials added beta blockade to background therapy that included ACE inhibitors and diuretics in more than 90% of patients. The trial results support benefit from both $beta_1$ selective and nonselective beta blockers, whether ancillary properties are present or not. Beta blocking agents with intrinsic sympathomimetic activity are likely to worsen survival and should be avoided in patients with HF.[29] The beta blockers that have been shown to be effective in clinical trials and their corresponding doses are shown in Table 7.1. Whenever possible, beta blockers proven to be efficacious in clinical trials should be used. A general summary of recommendations for the successful administration of beta blockers are provided in Table 7.2.

Nebivolol is a $beta_1$ selective beta blocker that is currently only approved for the treatment of hypertension in the United States (U.S.), but it does not have a Food and Drug Administration (FDA) approved indication for HF. Outcomes with nebivolol have recently been reported in the Study of the Effects of Nebivolol Intervention on Outcomes and Rehospitalization in Seniors with Heart Failure (SENIORS) trial. The study was a randomized trial in 2128 patients ≥70 years with a history of HF (a hospitalization for HF in the last year or an LVEF ≤35%). The primary endpoint of all-cause mortality or cardiovascular hospitalizations was reduced with nebivolol from 35.3% to 31.1% (HR 0.86, 95% CI 0.74−0.99, p = 0.039).[28] In contrast to other beta blocker trials, nebivolol did not significantly reduce all-cause mortality (HR 0.88, 95% CI 0.71−1.08, $P=0.21$).[28]

The randomized controlled trials of beta blockers were conducted in addition to ACE-inhibitor therapy. Thus, ACE-inhibitors have generally been initiated first, followed by beta-blockade. The Cardiac Insufficiency Bisoprolol Study III (CIBIS III) trial evaluated the effect of either bisoprolol or enalapril monotherapy for 6 months, followed by combination therapy on mortality and hospitalization.[30] The findings of this study suggested that the safety and efficacy of either approach (beta blocker initiation first or ACE-inhibitor initiation first) was similar.[30]

Recommendation

7.7 The combination of a beta blocker and an ACE inhibitor is recommended as routine therapy for asymptomatic patients with a LVEF ≤ 40%
- **Post-MI (Strength of Evidence = B)**
- **Non Post-MI (Strength of Evidence = C)**

Table 7.2. Summary of Recommendations for the Administration of Beta Blocker Therapy

General	• Initiate at low doses • Uptitrate gradually, generally no sooner than at 2-week intervals • Use target doses shown to be effective in clinical trials • Aim to achieve target dose in 8-12 weeks • Maintain at maximum tolerated dose
Considerations if symptoms worsen or other side effects appear	• Adjust dose of diuretic or other concomitant vasoactive medication • Continue titration to target dose after symptoms return to baseline • Considerations if uptitration continues to be difficult ○ Prolong titration interval ○ Reduce target dose ○ Consider referral to a HF specialist
If an acute exacerbation of chronic HF occurs	• Maintain therapy if possible • Reduce dosage if necessary • Avoid abrupt discontinuation • If discontinued or reduced, reinstate gradually before discharge

See Recommendations 7.10–7.11 and accompanying text for specific recommendations

Background

Randomized controlled data support the efficacy of ACE inhibitors in reducing both the likelihood of developing HF and the need for treatment or hospitalization in asymptomatic patients with an LVEF ≤35%.[31] Similar data are not available to support the use of beta blocker therapy in asymptomatic patients with reduced LVEF. Nevertheless, a number of arguments support the routine use of beta blockade in these patients. Guidance is provided by studies indicating the effectiveness of beta blocker therapy in patients following MI with good symptomatic and functional recovery, yet reduced LVEF.[31–33] These studies enrolled a number of patients without clinical HF. The Carvedilol Post-Infarct Survival Control in LV Dysfunction (CAPRICORN) study demonstrated a reduction in all cause mortality, cardiovascular mortality, and recurrent non-fatal MI for patients with post-MI reduced LVEF randomized to carvedilol.[34] Multiple studies suggest myocardial remodeling following beta blocker therapy in patients with symptomatic HF as well.[35–38]

Recommendation

7.8 Beta blocker therapy is recommended for patients with a recent decompensation of HF after optimization of volume status and successful discontinuation of intravenous diuretics and vasoactive agents, including inotropic support. Whenever possible, beta blocker therapy should be initiated in the hospital setting at a low dose prior to discharge in stable patients. (Strength of Evidence = B)

Background

Ongoing clinical experience and current trial data indicate that beginning beta blockade at low dose in the hospital is possible in patients with improved congestion and other symptoms.[39,40] Initiation of therapies in hospital is known to result in better utilization and the attainment of more optimal doses of a variety of cardiovascular drugs.[41,42]

Beta blocker therapy should not be initiated in patients with acute decompensated heart failure (ADHF) with persistent symptoms and congestion. However, many patients hospitalized for HF are NYHA functional class IV from volume overload, and will improve sufficiently with standard therapy to allow introduction of beta blockade. The Carvedilol Prospective Randomized Cumulative Survival Study (COPERNICUS) provides strong evidence in a prospective, randomized trial that patients with advanced HF, treated aggressively to reduce congestion and improve symptoms, benefit substantially from the introduction of beta blockade.[43]

Recommendations

7.9 Beta blocker therapy is recommended in the great majority of patients with HF and reduced LVEF, even if there is concomitant diabetes, chronic obstructive lung disease, or peripheral vascular disease. Beta blocker therapy should be used with caution in patients with diabetes with recurrent hypoglycemia, with asthma, or with resting limb ischemia. Considerable caution should be used if beta blockers are initiated in patients with marked bradycardia (<55 beats/min) or marked hypotension (systolic blood pressure <80 mm Hg). Beta blockers are not recommended in patients with asthma with active bronchospasm. (Strength of Evidence = C)

7.10 It is recommended that beta blockade be initiated at low doses and uptitrated gradually, typically at 2-week intervals in patients with reduced LVEF, and after 3-10 day intervals in patients with reduced LVEF following newly diagnosed MI. (Strength of Evidence = B)

7.11 It is recommended that beta blocker therapy be continued in most patients experiencing a symptomatic exacerbation of HF during chronic maintenance treatment, unless they develop cardiogenic shock, refractory volume overload, or symptomatic bradycardia (Strength of Evidence = C)

A temporary reduction of dose (generally by one-half) in this setting may be considered. Abrupt discontinuation in patients with symptomatic exacerbation should be avoided, unless the situation is life-threatening. (Strength of Evidence = C)

If discontinued or reduced, beta blockers should be reinstated before the patient is discharged. In

general, doses should be uptitrated to the previous well-tolerated dose as soon as safely possible (Strength of Evidence =B)

Background

The beta blockers studied in clinical trials are now established as routine therapy in patients with reduced LVEF. This therapy is well tolerated by a large majority of patients with HF, even those with comorbid conditions like diabetes mellitus,[44,45] chronic obstructive lung disease[46] and peripheral vascular disease.[47]

Clinical trials of beta blockers in HF have been conducted by uptitrating beta blockers to a maximum tolerated dose rather than titrating to a reduction in heart rate. Recent meta-analyses of previous trials suggest that the magnitude of benefit of beta blockers may be related to the reduction in heart rate rather than the dose of beta blocker.[48–51] However, until further data are available the current recommendation to uptitrate to doses of beta blockers used in randomized clinical trials will remain unchanged. In trials of chronic HF with reduced LVEF, beta blockers were initiated at low doses and uptitrated gradually, typically at 2-week intervals.[24–27] In patients with reduced LVEF following newly diagnosed MI, beta blockers were initiated at low disease and uptitrated after 3–10 day intervals.[34] Doses found to be effective in HF trials are generally achieved in 8 to 12 weeks. Patients developing worsening HF symptoms or other side effects during titration may require a dosage adjustment of diuretic or concomitant vasoactive medications. If side effects resolve with medication adjustment, patients can subsequently be titrated to target or maximally tolerated doses. Some patients may require a more prolonged interval during uptitration, a temporary reduction in beta blocker dose, or, in rare cases, withdrawal of therapy. If switching from a non-evidence based beta blocker to an evidence-based beta blocker, wait 24 hours from the last dose of a once-daily agent or wait 12 hours from the last dose of a twice-daily agent before beginning an evidence-based beta blocker.[52] The dose of the evidence-based beta blocker should be the equivalent of one-half the non evidence-based dose for most patients, although lower initial doses may be clinically appropriate for some patients; then uptitrate to target dose at 2-week intervals.[52]

Clinical deterioration during stable maintenance therapy with beta blockers rarely is related to administration of these agents. Nonadherence to medications, progression of underlying LV dysfunction and the adverse influence of a number of comorbid factors, including the occurrence of ischemia, hemodynamic instability from arrhythmia, and pulmonary complications such as pneumonia, are much more likely to be responsible for clinical deterioration. The best course is to use standard therapy to relieve congestion and treat exacerbating factors, rather than reduce or discontinue beta blockade. A retrospective review of patients enrolled in the Outcomes of a Prospective Trial of Intravenous Milrinone for Exacerbations of Chronic Heart Failure (OPTIME-CHF) trial of patients hospitalized with ADHF, found that continuation of beta blockade did not interfere with symptomatic improvement during admission,[53] supporting the continuation of beta blockade in patients hospitalized with an episode of decompensation. This same observation was made in the Evaluation Study of Congestive Heart Failure and Pulmonary Artery Catheterization Effectiveness (ESCAPE) trial.[54] In the Carvedilol or Metoprolol European Trial (COMET), patients whose beta blocker was discontinued or the dose reduced during a HF hospitalization had a higher mortality at 1 and 2 years as compared to patients whose therapy was continued.[55] Data from the Organized Program to Initiate Lifesaving Treatment in Hospitalized Patients with Heart Failure (OPTIMIZE-HF) registry also demonstrated an association between lower post-discharge mortality risk and continuation of beta blocker therapy during a HF hospitalization, even after adjustment for other prognostic factors.[56]

The Beta-blocker Continuation Versus Interruption in Patients with Congestive Heart Failure Hospitalized for a Decompensation Episode (B-CONVINCED) study was a randomized, controlled, open label trial of beta-blockade continuation versus discontinuation in 169 patients with acutely decompensated HF and LVEF $<40\%$.[57] There was no difference between groups in general well-being or dyspnea at either day 3 or day 8 after randomization. Length of hospital stay was not different between groups, and there was no difference in in-hospital mortality or death or rehospitalization at 3 months. The proportion of patients receiving beta blockade at 3 months was higher for patients who were maintained on beta blockade during the hospitalization (90% vs. 76%, $P=0.04$).[57]

Abrupt withdrawal of beta blockade should be avoided, especially in patients with coronary artery disease. Studies of the withdrawal of beta blockade in patients with reduced LVEF, but improved and stable clinical HF, have revealed a substantial risk of worsening HF and early death after beta blocker discontinuation.[58,59]

In certain patients, frequent return visits for dose titration may be difficult to accommodate in a busy clinical practice. Trained personnel, including nurse practitioners, physician assistants, and pharmacists, with physician supervision, may more efficiently perform patient education and reevaluation during uptitration. HF specialty programs are more likely to have the resources to provide this follow-up and education.[60] Patients should be aware that symptomatic deterioration is possible early in therapy and that symptomatic improvement may be delayed weeks to months.

Referral to clinicians with HF expertise may be helpful for patients who do not have contraindications to beta blockade (such as symptomatic bradycardia), but who have difficulty initiating, uptitrating or maintaining beta blocker therapy. Several factors may contribute to difficulty in using beta blocker therapy, including recent or multiple

HF hospitalizations; HF associated with ischemia, uncontrolled hypertension, moderate −severe valvular disease, syncope, or renal dysfunction; other multiple, active comorbidities, including asthma and chronic obstructive pulmonary disease; intolerance to other recommended HF drug therapies; persistent poor adherence to the HF plan of care; low output state; and persistent NYHA class III or IV symptoms.

Implantation of Cardiac Pacemakers in Patients With Baseline Bradycardia: An Unresolved Issue

Given the strength of evidence supporting beta blocker therapy in patients with symptomatic HF, some physicians would consider pacemaker implantation when symptomatic bradycardia or heart block occurs during the initiation of this therapy. No clinical trial data are available to support this practice. Data from a decision analysis/cost-effectiveness modeling study suggested that prophylactic pacemaker insertion to allow beta blocker treatment in patients with bradycardia may be associated with clinical benefits, and may be cost-effective.[14] However, this approach cannot be recommended in the absence of clinical data.[6,14] It should be recognized that right ventricular (RV) pacing alone may result in deterioration of ventricular function, negating any potential benefit from beta blockade.[61] Consideration should be given to the withdrawal of other drugs that may have bradycardic effects.

Angiotensin Receptor Blockers (Table 7.1)

See recommendation 7.2-7.5 and the accompanying background for a discussion of the role of ARBs as an alternative to ACE-inhibitors.

Recommendations

7.12 The routine administration of an ARB is not recommended in addition to ACE inhibitor and beta blocker therapy in patients with a recent acute MI and reduced LVEF. (Strength of Evidence = A)

7.13 The addition of an ARB should be considered in patients with HF due to reduced LVEF who have persistent symptoms or progressive worsening despite optimized therapy with an ACE inhibitor and beta blocker. (Strength of Evidence = A)

Background

Post-MI Studies. The VALIANT trial evaluated the clinical effectiveness of ACE inhibitors and ARBs in patients with a recent MI (0.5-14 days), an LVEF ≤40% and clinical or radiographic signs of HF.[16] The addition of valsartan to captopril did not result in a significant improvement in total mortality or cardiovascular mortality compared to captopril alone, and there were more drug-related adverse events in the valsartan-captopril group.

The Optimal Trial in Myocardial Infarction with Angiotensin II Antagonist Losartan (OPTIMAAL) was designed to prove that losartan would be superior or not inferior to captopril in decreasing all-cause mortality in patients with MI complicated by reduced LVEF.[17] There was a trend toward decreased all-cause mortality in the captopril group compared with losartan, and fewer captopril-treated patients experienced sudden death or a resuscitated cardiac arrest.[17] The addition of losartan to captopril did not result in a significant improvement in total mortality or cardiovascular mortality compared with captopril alone, and there were more drug-related adverse events in the losartan-captopril group.

The results of VALIANT cannot be directly compared with those of Val-HeFT and CHARM, because VALIANT was conducted in patients with recent MI and both an ACE inhibitor and ARB were added, rather than adding the ARB to a stable patient on chronic ACE inhibitor therapy. These data suggest that an ARB may be beneficial when added to an ACE inhibitor and beta blocker in patients with chronic HF, but not in those with HF because of a recent MI. See Recommendations 7.21 and 7.22 and accompanying background for more information on the optimal use of multi-drug therapy.

Aldosterone Antagonists (Table 7.1)

Recommendations

7.14 Administration of an aldosterone antagonist is recommended for patients with NYHA class IV (or class III, previously class IV) HF from reduced LVEF (<35%) while receiving standard therapy, including diuretics. (Strength of Evidence = A)

7.15 Administration of an aldosterone antagonist should be considered in patients following an acute MI, with clinical HF signs and symptoms or history of diabetes mellitus, and an LVEF <40%. Patients should be on standard therapy, including an ACE inhibitor (or ARB) and a beta blocker. (Strength of Evidence = A)

7.16 Aldosterone antagonists are not recommended when creatinine is >2.5 mg/dL (or creatinine clearance is <30 ml/min) or serum potassium is >5.0 mmol/L or in conjunction with other potassium-sparing diuretics. (Strength of Evidence = A)

7.17 It is recommended that serum potassium concentration be monitored frequently following initiation or change in an aldosterone antagonist. Monitoring should reflect protocols followed in clinical trials. (Strength of Evidence = A)

7.18 In the absence of persistent hypokalemia (<4.0 mmol/L), supplemental potassium is not recommended in patients taking an aldosterone antagonist. (Strength of Evidence = A)

Background

Sustained activation of aldosterone appears to play an important role in the pathophysiology of HF.[62] Increased renin and angiotensin II levels contribute to the stimulation of aldosterone secretion. Elevated circulating levels of this hormone enhance sodium retention and potassium and magnesium loss. Aldosterone upsets autonomic balance by increasing sympathetic activation and parasympathetic inhibition and promotes cardiac and vascular structural remodeling through collagen synthesis.[63–65]

Although ACE inhibition may transiently decrease aldosterone secretion, there are diverse stimuli other than angiotensin II for the production of this hormone.[66] Studies suggest a rapid return of aldosterone to levels similar to those before ACE inhibition.[67] The potential pathophysiologic role of aldosterone and the results of a pilot study that suggested low doses of spironolactone were tolerated in HF, led to additional investigation of these agents in severe HF and subsequently in post-MI HF.[68,69]

The Randomized Aldactone Evaluation Study (RALES) was designed to determine the effect of low-dose spironolactone on survival in severely symptomatic (recent or current NYHA class IV) HF patients treated with an ACE inhibitor, loop diuretic, and, in many cases, digoxin.[68] The study enrolled a total of 1663 patients with reduced LVEF (LVEF ≤35%) resulting from ischemic and nonischemic etiologies. All-cause mortality was the prespecified primary endpoint. There were 386 (46%) deaths in the placebo group compared with 284 (35%) in the spironolactone group. The risks of sudden death or of death from progressive HF were both reduced. The frequency of hospitalization for HF was 35% lower in patients treated with spironolactone compared with placebo. Greater improvement was noted in NYHA functional class in those receiving spironolactone. Because deaths in class III patients were designated as a worsening in NYHA class, this functional improvement likely reflects the mortality benefit of the drug.

The inclusion and exclusion criteria for the RALES trial are important to consider when applying the study results to clinical practice. The yearly mortality rate in the placebo group was high, reflecting the advanced HF of study participants. The potential benefit of aldosterone antagonists in patients with milder HF and lower risk cannot be determined from RALES data. It should be noted that only 10% of placebo and 11% of spironolactone patients in the RALES trial were treated with beta blocker therapy. Patients with potassium levels >5.0 mmol/L were excluded, as were patients with abnormal renal function, defined as a creatinine >2.5 mg/dL. Patients recruited into the trial met the potassium inclusion criteria despite the frequent concomitant use of potassium supplementation at baseline (28%). Adhering to these patient characteristics may be necessary to avoid excessive hyperkalemia during spironolactone treatment. In clinical practice, a more conservative approach to serum creatinine may be warranted. The recommended serum creatinine cutoff of 2.5 mg/dL in this guideline is consistent with the eligibility criteria for the RALES trial. However, the majority of patients enrolled in RALES had a serum creatinine below this level. In addition, several groups including women, the elderly, or patients with low muscle mass may have a lower creatinine clearance for a given level of serum creatinine. For these patients, it may be reasonable to calculate an estimated creatinine clearance rather than relying solely on the serum creatinine value. Aldosterone antagonists are not recommended in patients with creatinine clearance <30 ml/min.

Spironolactone should be used in conjunction with standard therapy, including ACE inhibitors, digoxin, diuretics, and beta blockers. It should be initiated at a dose of 12.5 to 25 mg per day. Spironolactone can be titrated to 37.5 mg or 50 mg with careful monitoring in patients with refractory HF or persistent hypokalemia. Serum potassium and creatinine should be monitored closely in the first few weeks of therapy. If the serum potassium exceeds 5.0 mmol/L, then the dose of spironolactone should be decreased to 25 mg every other day and medications that could contribute to hyperkalemia should be adjusted. The risk of hyperkalemia with aldosterone antagonism is increased in patients with older age, diabetes, higher serum creatinine levels, and higher ACE inhibitor doses. In community settings the risk is far higher than documented during careful monitoring in trial settings, and may be as high as 20% .[70] This risk should be taken into careful consideration when treating with an aldosterone antagonist, and remains present even after successful initiation of this therapy. Patients should continue to be monitored carefully and should be instructed not to take the aldosterone antagonist during any circumstances of volume loss such as gastroenteritis.

In addition to hyperkalemia, gynecomastia or breast pain may be important side effects of spironolactone, but not eplerenone. They were reported in 10% of the men randomized to spironolactone versus 1% of the males in the placebo group in the RALES trial. These side effects were more frequent in patients taking digoxin.

Clinical studies with the selective aldosterone antagonist, eplerenone, have demonstrated favorable results in patients with HF after acute MI. A multicenter, randomized, double-blind, placebo-controlled trial, Eplerenone Post-Acute Myocardial Infarction Heart Failure Efficacy and Survival Study (EPHESUS), tested the effect of eplerenone versus placebo in 6642 patients.[69] Patients were enrolled after an acute MI if they had an LVEF ≤40% and HF documented by signs and symptoms. HF signs and symptoms were not required if patients had diabetes. Exclusion criteria for the study included creatinine >2.5 mg/dL and serum potassium >5.0 mmol/L. Patients were generally receiving agents shown to be effective in reducing risk in patients after acute MI, including beta blockers, ACE inhibitors, aspirin and cholesterol-lowering agents. The hypothesis was that eplerenone would reduce overall mortality and cardiovascular mortality or hospitalization.

The results, after an average follow-up 16 months, revealed a statistically significant reduction in cardiovascular mortality or hospitalization and all-cause mortality and hospitalization in the group receiving eplerenone.[69] The reduction in all-cause mortality was observed as early as 30 days after randomization.[71] There was also a significant reduction in sudden cardiac death favoring eplerenone treatment.

Adverse reactions to eplerenone were uncommon. As with spironolactone, serious hyperkalemia was more prevalent with eplerenone treatment. It should be noted that baseline serum potassium concentration in both the eplerenone and placebo groups was 4.3 mmol/L. As outlined in the recommendation for use, it is important to monitor electrolytes, especially potassium. The major predictors of hyperkalemia in EPHESUS were estimated glomerular filtration rate (eGFR) <60 ml/min, baseline serum potassium above the median (4.3 mEq/L), diabetes mellitus, and prior use of antiarrhythmic drugs. The effect of eplerenone on all-cause mortality was not affected by baseline serum potassium or the change in serum potassium from baseline.[72] Post-hoc analyses suggested that patients who were not on ACE inhibitors or ARBs and beta blockers had less benefit from the addition of eplerenone than those on these neurohormonal antagonists.[69] A recent systematic review of post-MI and HF studies in subjects with reduced LVEF using the aldosterone antagonists spironolactone, eplerenone, and canrenoate confirmed benefits in all-cause mortality, hospitalizations, and LVEF.[73]

Remodeling Post MI Another study randomized 134 patients post-anterior MI after revascularization to spironolactone versus placebo.[74] All patients were on ACE inhibitors. After 1 month, LVEF was improved, end-diastolic dimension was reduced, and markers of collagen synthesis were reduced in the spironolactone group, indicating an improvement in LV remodeling after MI. One of the limitations of this study was that only 31% of patients were on beta blockers. A substudy of EPHESUS demonstrated lower levels of collagen biomarkers among patients randomized to eplerenone, suggesting that it suppresses post-MI remodeling.[75]

Aldosterone Antagonists in Mild to Moderate HF. Patients enrolled in RALES had chronic severe HF (NYHA IV at enrollment or in the past). EPHESUS studied patients who were post-MI. Aldosterone antagonists have not been proven effective in patients with mild to moderate HF in the absence of recent MI or in patients with HF and preserved LV systolic function.

Selective Versus Nonselective Aldosterone Antagonists. The efficacy of selective and nonselective aldosterone antagonists is generally considered to be equivalent. The potential advantage of a selective aldosterone blocker that blocks only the mineralocorticoid receptor is a reduction in side effects. A nonselective blocker, such as spironolactone, blocks the mineralocorticoid, glucocorticoid, androgen, and progesterone receptors, resulting in potential gynecomastia and sexual dysfunction. The incidence of gynecomastia with eplerenone in EPHESUS was 0.5%, whereas it was 10% with spironolactone in RALES.[68,69]

Hyperkalemia. Hyperkalemia is a life-threatening complication of aldosterone antagonists and is much more likely to occur in patients with diabetes or renal insufficiency or in those taking ACE inhibitors or ARBs. When more than one of these risk factors is present, the likelihood of hyperkalemia increases. In RALES and EPHESUS, aldosterone antagonists were not initiated if the creatinine was >2.5 mg/dL or serum potassium was >5.0 mmol/L. In RALES, the potassium was monitored every 4 weeks for 12 weeks, every 3 months up to a year, and every 6 months after the first year. In the EPHESUS trial, in which patients were taking a larger number of concomitant medications, potassium was measured at 48 hours, at 4-5 weeks, and then every 3 months. Potassium was measured 1 week after a dose increase of an aldosterone antagonist. Although patients with creatinine <2.5 mg/dL were enrolled in the clinical trials, very few patients actually had a creatinine >1.7 mg/dL. Thus additional monitoring should be considered in these patients.

Few patients will tolerate an aldosterone antagonist in the absence of concomitant therapy with a potassium-wasting diuretic. Potassium supplements and potassium-containing salt supplements should be reduced or, if possible, discontinued. Serum potassium monitoring should be at least as rigorous as in RALES and EPHESUS and more rigorous in patients with multiple risk factors. Nonsteroidal antiinflammatory agents, including cyclooxygenase-2 inhibitors, should be avoided because they may worsen renal insufficiency, increasing the risk of hyperkalemia.

Renin Inhibitors

Aliskiren is an orally active renin inhibitor that appears to suppress the RAAS to a similar degree as ACE-inhibitors.[76] The Aliskiren Observation of Heart Failure Treatment (ALOFT) study evaluated aliskiren in addition to an ACE-inhibitor in patients with NYHA class II-IV HF. The primary endpoint was the change from baseline to 3 months in N-terminal prohormone brain natriuretic peptide (NT-proBNP). NT-proBNP was lower for patients randomized to aliskiren, whereas it was higher for patients randomized to placebo ($P=0.01$).[77,78] Phase 3 trials to evaluate the effects of aliskiren on mortality and morbidity are ongoing.

Oral Nitrates and Hydralazine

Recommendations

7.19 A combination of hydralazine and isosorbide dinitrate is recommended as part of standard therapy in addition to beta blockers and ACE inhibitors

for African Americans with HF and reduced LVEF.

- **NYHA III or IV HF (Strength of Evidence = A)**
- **NYHA II HF (Strength of Evidence = B) (See Section 15: Special Populations)**

7.20 A combination of hydralazine and isosorbide dinitrate may be considered in non-African-American patients with HF and reduced LVEF who remain symptomatic despite optimized standard therapy. (Strength of Evidence = C)

Background

The Vasodilator Heart Failure Trial (V-HeFT) was the first major randomized HF trial and was conducted in Veterans Administration hospitals throughout the US. Patients who remained symptomatic with mild to severe symptoms of HF despite treatment with diuretics and digoxin were randomized to a combination of hydralazine and isosorbide dinitrate or prazosin or placebo. The combination of hydralazine and isosorbide dinitrate was associated with a reduction in all-cause mortality compared to both placebo and prazosin that was of borderline statistical significance ($P = .053$).[79] In V-HeFT II, the combination of hydralazine and isosorbide dinitrate was compared with enalapril in a population similar to V-HeFT I.[80] All-cause mortality was 28% lower with enalapril than with the hydralazine isosorbide dinitrate combination. However, quality of life and peak exercise capacity as measured by peak oxygen consumption were better with hydralazine-isosorbide dinitrate.

The African-American Heart Failure Trial (A-HeFT) enrolled 1050 self-identified African-American patients who had NYHA class III or IV HF with dilated ventricles and reduced LVEF.[81] In this placebo-controlled, blinded, and randomized trial, subjects were randomly assigned to receive a fixed combination of isosorbide dinitrate plus hydralazine or placebo in addition to standard therapy for HF. The primary end point was a composite score made up of weighted values for death from any cause, a first hospitalization for HF, and change in the quality of life. The study was terminated early because of a significantly higher mortality rate in the placebo group than in the group given the fixed combination of isosorbide dinitrate plus hydralazine (10.2% vs 6.2%, $P = .02$). The mean primary composite score was significantly better in the group given isosorbide dinitrate plus hydralazine than in the placebo group, as were its individual components: 43% reduction in the rate of death from any cause, 33% relative reduction in the rate of first hospitalization for HF, and an improvement in the quality of life. These results taken together constitute a strong recommendation for the addition of the fixed combination of isosorbide dinitrate/hydralazine to the standard medical regimen for HF in African Americans. Data cannot exclude a benefit of the isosorbide dinitrate/hydralazine combination in non-African Americans when added to the standard medical regimen for HF.

Optimal Use of Multi-Drug Therapy

Recommendations

7.21 Additional pharmacologic therapy should be considered in patients with HF and reduced LVEF who have persistent symptoms or progressive worsening despite optimized therapy with an ACE inhibitor and beta blocker. The choice of specific agent will be influenced by clinical considerations, including renal function status, chronic serum potassium concentration, blood pressure, and volume status. The triple combination of an ACE inhibitor, an ARB, and an aldosterone antagonist is not recommended because of the high risk of hyperkalemia. (Strength of Evidence = C)

- **Addition of an ARB. (Strength of Evidence = A)**
- **Addition of an aldosterone antagonist:**
  - **for severe HF (Strength of Evidence =A)**
  - **for moderate HF (Strength of Evidence = C)**
  - **for post-MI HF (Strength of Evidence = A)**
- **Addition of the combination of hydralazine/isosorbide dinitrate:**
  - **for African Americans (Strength of Evidence = A)**
  - **for others (Strength of Evidence = C)**

7.22 Additional pharmacological therapy should be considered in patients with HF and reduced LVEF *who are unable to tolerate a beta blocker* and have persistent symptoms or progressive worsening despite optimized therapy with an ACE inhibitor. The choice of specific agent will be influenced by clinical considerations, including renal function status, chronic serum potassium concentration, blood pressure and volume status. The triple combination of an ACE inhibitor, an ARB, and an aldosterone antagonist is not recommended due to the high risk of hyperkalemia. (Strength of Evidence = C)

- **Addition of an ARB. (Strength of Evidence = C)**
- **Addition of an aldosterone antagonist:**
  - **for severe HF (Strength of Evidence = C)**
  - **for moderate HF (Strength of Evidence = C)**
- **Addition of the combination of hydralazine/isosorbide dinitrate:**
  - **for African Americans (Strength of Evidence = C)**
  - **for others (Strength of Evidence = C)**

Background

Multi-drug therapy is required for optimal management to slow progression and improve outcome in patients with HF and reduced LVEF. An ACE inhibitor plus a beta blocker is standard background therapy. An ARB can be substituted for an ACE inhibitor if clinically indicated. An ARB can be added to an ACE inhibitor in individuals in whom beta blocker is contraindicated or not tolerated. The optimal choice of additional drug therapy to further improve outcome in patients already treated with 2 of these 3 drugs is not firmly established. An aldosterone inhibitor, an ARB (if the patient is already on an ACE inhibitor) and the combination of isosorbide dinitrate and hydralazine have all been shown to exert further benefit in controlled trials, but have not been the subject of comparative trials. The choice among these agents may be influenced by the patient's age, renal function, serum potassium, racial background, and severity of the clinical syndrome. Certain combinations would require careful monitoring. For example, if an ARB or aldosterone antagonist were combined with an ACE inhibitor, with or without beta blocker therapy, elderly patients would require close monitoring of serum potassium, especially those with diabetes or renal insufficiency.

The use of 4 or more of these drugs in combination cannot be recommended on the basis of clinical trial evidence for additional efficacy, but such combinations have been used in subsets of patients enrolled in clinical trials. In the CHARM-Added trial, an ARB was safely administered to patients receiving an ACE inhibitor, beta blocker and aldosterone inhibitor, when patients were closely monitored for hyperkalemia and worsening renal function.[82] Non-significant increases in serum creatinine and serum potassium have been observed in clinical trials, and clinicians must closely monitor patients for these adverse effects when using these drugs in combination. In the A-HeFT study, black patients were given isosorbide dinitrate-hydralazine in addition to an ACE inhibitor, an ARB, and an aldosterone inhibitor with no apparent adverse effect.[81] Nonetheless, the use of combinations of 4 or more of these drugs would not be based on evidence for further efficacy and should mandate close monitoring of blood pressure, renal function, and serum potassium.

As discussed previously in this section, ARBs, aldosterone antagonists, and hydralazine/isosorbide dinitrate all have been shown to be beneficial in patients with chronic HF with or without beta blocker therapy. However, no study has specifically evaluated patients who are intolerant to beta blockers. Those who are intolerant due to hypotension or worsening HF are likely to have more severe HF and to be at higher risk of hypotension, worsening renal function, or hypokalemia with additional medical therapy. Thus closer clinical and laboratory monitoring is important.

Diuretic Therapy

Recommendation

7.23 Diuretic therapy is recommended to restore and maintain normal volume status in patients with clinical evidence of fluid overload, generally manifested by congestive symptoms (orthopnea, edema, and shortness of breath), or signs of elevated filling pressures (jugular venous distention, peripheral edema, pulsatile hepatomegaly, and, less commonly, rales). (Strength of Evidence = A) Loop diuretics rather than thiazide-type diuretics are typically necessary to restore normal volume status in patients with HF. (Strength of Evidence = B)

Background

Loop and distal tubular diuretics are necessary adjuncts in the medical therapy for HF when symptoms are the result of sodium and water retention. Diuretics reduce congestive symptoms and signs and can be titrated as needed to restore euvolemia and to reach an estimated "dry" weight goal for the patient.

Relief of signs and symptoms must be achieved without causing side effects, particularly symptomatic hypotension or worsening renal function. Underutilization of diuretic therapy is common, but excessive diuresis is also problematic, limiting ventricular preload and producing excessive lowering of blood pressure, especially in conjunction with antihypertensive drugs such as ACE inhibitors, ARBs, and beta blockers. Diuretic administration should be accompanied by a recommendation for dietary sodium restriction to between 2000 and 3000 mg daily for the typical patient with HF (see Section 6). Fluid restriction is best reserved for the patient refractory to diuretics with a high oral fluid intake or symptomatic hyponatremia.

Although some retrospective analyses have generated concern about the long-term safety of diuretics,[83,84] this concern is not supported by any controlled data. There are few controlled studies of diuretics because few symptomatic patients can be managed without them. Still, there are data to support the safety and efficacy of diuretics.[85] A trial in which patients with stable and relatively mild HF without evidence of significant volume overload were randomized to substitution of an ACE inhibitor or continued diuretic showed that the large majority of patients required reinstatement of diuretic therapy.[86] Very small trials suggest that in patients with reduced LVEF with or without HF, ACE inhibitor therapy may prevent remodeling more than diuretics, but that diuretics may be superior for symptom improvement.[87,88] However, there are no controlled clinical trial data prospectively evaluating the overall impact of diuretic therapy on mortality in patients with HF.

Diuretics may cause activation of the RAAS, potentiate hypotensive effects of ACE inhibitors,[89,90] and may decrease cardiac output, especially in patients with diastolic LV dysfunction. Diuretics also may induce hypokalemia and hypomagnesemia.

Loop Diuretics. Loop diuretics, which act on the ascending limb of the renal medullary loop of Henle, are considered the diuretic class of choice for the treatment of HF. These drugs produce a greater fractional excretion of filtered sodium than is induced by thiazide-type diuretics. The onset of action with intravenous administration is within minutes, making this route of administration preferable for the acutely symptomatic or hospitalized patient (see Section 12).

Thiazide Diuretics. Thiazide diuretics, which inhibit sodium reabsorption in the distal renal tubule, may be effective as monotherapy in HF patients with mild volume overload and preserved renal function. They are generally superior to loop diuretics as antihypertensive agents. They are delivered to their site of action by filtration and are ineffective when the glomerular filtration rate falls below 30 mL/min.

Potassium-Sparing Diuretics. Potassium-sparing diuretics, other than aldosterone antagonists, have no direct diuretic activity. Several are formulated in combination with thiazides for the treatment of hypertension, but are not generally useful in HF. For patients with excessive potassium losses on loop diuretics, coincident administration of these agents can be helpful. However, because of their beneficial effects on prognosis and ability to facilitate diuresis, aldosterone antagonists are preferred for this purpose. The use of these agents for purposes other than as a diuretic is discussed earlier in this section. Table 7.3 and Table 7.4 provide dosage and other information about loop diuretics, thiazides, and potassium-sparing diuretics.[6,91,92]

Recommendation

7.24 The initial dose of diuretic may be increased as necessary to relieve congestion. Restoration of normal volume status may require multiple adjustments over many days and occasionally weeks in patients with severe fluid overload evidenced by massive edema or ascites. After a diuretic effect is achieved with short-acting loop diuretics, increasing administration frequency to twice or even 3 times per day will provide more diuresis with less physiologic perturbation than larger single doses. (Strength of Evidence = B)

Oral torsemide may be considered in patients in whom poor absorption of oral medication or erratic diuretic effect may be present, particularly those with right-sided HF and refractory fluid retention despite high doses of other loop diuretics. (Strength of Evidence = C)

Intravenous administration of diuretics may be necessary to relieve congestion. (Strength of Evidence = A)

Diuretic refractoriness may represent patient nonadherence, a direct effect of diuretic use on the kidney, or progression of underlying cardiac dysfunction.

Background

HF can adversely affect the pharmacokinetics of diuretics in a number of ways. Delayed absorption, resulting from gut edema from high central venous pressure, can reduce peak serum concentration. The volume of distribution is variable in the setting of chronic HF. Relative hypotension or reduced cardiac output producing a limitation in renal blood flow reduces the delivery of diuretic to the kidney. In general, these limitations can be overcome by successively increasing the dose administered.

Recommendation

7.25 Addition of chlorothiazides or metolazone, once or twice daily, to loop diuretics should be considered in patients with persistent fluid retention despite high-dose loop diuretic therapy. But chronic daily use, especially of metolazone, should be avoided if possible because of the potential for electrolyte shifts and volume depletion. These drugs may be used periodically (every other day or weekly) to optimize fluid management. Metolazone will generally be more potent and much longer-acting in this setting and in patients with chronic renal insufficiency, so administration should be adjusted accordingly. Volume status and electrolytes must be monitored closely when multiple diuretics are used. (Strength of Evidence = C)

Background

Thiazide-type diuretics can be used in combination with loop diuretics to augment natriuresis when high doses of loop diuretic are ineffective at restoring euvolemia. Improved natriuresis from the combination of these 2 classes of diuretics is expected as they act at different sites in the kidney to produce sodium loss. In addition, resistance to loop diuretics can occur, partially due to progressive hypertrophy of distal renal tubular endothelial cells. This results in greater distal tubular reabsorption of sodium, which in turn reduces the net natriuretic effect of loop diuretics. Combining a thiazide-type diuretic with a loop diuretic typically will overcome this compensatory hypertrophy and result in a significantly greater diuretic effect. Metolazone is a thiazide-like diuretic with better oral availability than loop diuretics. It has a half-life of approximately 14 hours.

Table 7.3. Loop Diuretics

Agent	Initial Daily Dose (mg)	Maximum Total Daily Dose (mg)	Elimination	Duration of Action (hr)
Furosemide*	20−40 mg qd or bid	600 mg	65%R 35%M	4−6
Bumetanide*	0.5−1.0 mg qd or bid	10 mg	62%R 38%M	6−8
Torsemide*	10−20mg qd	200 mg	20%R 80%M	12−16
Ethacrynic acid*,+	25−50 mg qd or bid	200 mg	67%R 33%M	6

Equivalent doses: furosemide 40 mg = bumetanide 1 mg = torsemide 20 mg = ethacrynic acid 50 mg.
R = renal; M = metabolic; B = excreted into bile; U = unknown.
*Available for oral or intravenous administration (no dosage adjustments).
+Non-sulfa containing, may be used in sulfa-allergic patients.

Table 7.4. Other Diuretics

Agent	Initial Daily Dose (mg)	Maximum Total Daily Dose (mg)	Elimination	Duration of Action (hr)
Thiazides				
Chlorothiazide*	250−500 qd or bid	1000 mg	R	6−12
Chlorthalidone	12.5−25 mg qd	100 mg	65%R 10%B 25%U	24−72
Hydrochlorothiazide	25 mg qd or bid	200 mg	R	6−12
Metolazone	2.5 mg qd	20 mg	80%R 10%B 10%U	12−24
Idapamide	2.5 mg qd	5 mg	M	36
*May be given IV in doses of 250−1000 mg.				
Potassium-Sparing				
Spironolactone*	12.5−25 qd	50 mg*	M	48−72
Eplerenone*,+	25−50 qd	100 mg*	R, M	
Amiloride	5 qd	20 mg	R	24
Triamterene	50−75 bid	200 mg	M	7−9

R = renal; M = metabolic; B= excreted into bile; U = unknown.
*Higher doses have been used to control volume retention or hyperkalemia but close monitoring is mandatory.
+Do not use if creatinine clearance is ≤30 mL/min or with cytochrome 3A4 inhibitors.

The diuretic effects of metolazone are preserved even in patients with reduced GFR (<20 ml/min) because it does not decrease GFR or renal plasma flow; in contrast, thiazide diuretics can decrease GFR which contribute to their lower efficacy in patients with renal impairment.

Recommendation

7.26 Careful observation for the development of side effects, including electrolyte abnormalities, symptomatic hypotension, renal dysfunction, or worsening renal function, is recommended in patients treated with diuretics, especially when used at high doses and in combination. Patients should undergo routine laboratory studies and clinical examination as dictated by their clinical response. (Strength of Evidence = B)

Background

Hypokalemia from excessive potassium wasting is common during loop diuretic therapy, especially during the reversal of significant volume overload. Thiazide-type diuretics also contribute to potassium wasting. Serum potassium concentration should be monitored when diuretics are used, particularly during initiation and uptitration of therapy, with supplements given as needed. Other electrolyte disturbances associated with chronic diuretic use include hypomagnesemia and hypocalcemia.

Excessive diuresis may lead to volume depletion during treatment. Symptoms may include fatigue and shortness of breath, rather than the more predictable symptoms of lightheadedness. Hyperkalemia may accompany mild volume depletion and is more likely to occur in patients receiving ACE inhibitors, ARBs, and/or aldosterone blockers, especially in patients with diabetes or those taking potassium supplements or ingesting foods with high potassium content.

Use of loop and distal tubular diuretics in combination may be necessary to relieve symptoms, but may result in excessive volume loss and electrolyte disturbance. Distal tubular diuretics should be introduced cautiously when they are combined with loop diuretics, and patients should be monitored closely for side effects. Initially, only single low doses (eg, metolazone 2.5 mg) should be administered to determine the magnitude of response. If necessary, higher doses may be used subsequently, but this should be done cautiously with close monitoring of electrolytes and volume status. Twice-daily dosing of distal agents is generally not helpful because they have a long duration of action. In most cases, the frequency of use can be cut back to every other day, once or twice weekly, or as needed based on a weight threshold.

Worsening renal function is common with excessive diuresis, especially when patients are receiving ACE inhibitors or ARBs. Fortunately, reduction in diuretic dose and restoration of euvolemia will return renal function to

baseline levels in almost all cases unless hypovolemia has been prolonged or worsening renal function is due to another cause (eg, nephrotoxic drugs, post-obstructive uropathy). Intensification of diuretic therapy in these patients may be accompanied by a worsening of renal function reflected by modest elevations in blood urea nitrogen and serum creatinine concentration. Some reduction in renal function may be a necessary tradeoff for symptom relief in this setting. While there is an association between worsening renal function and adverse outcomes in HF, causality remains unproven.

The occurrence of reduced renal function should prompt a review of the patient's current medications to avoid concomitant administration of nephrotoxic drugs or drugs that reversibly affect renal function (eg, nonsteroidal anti-inflammatory drugs, antibiotics) and to determine if dose reduction in medications dependent on renal clearance (eg, digoxin) is warranted. It is essential to recognize progressive renal insufficiency from decreasing renal perfusion that will require adjustment of diuretic therapy. Worsening renal function can also result from inadequate diuresis and volume overload leading to renal venous or intraabdominal hypertension.

Loop diuretics may be associated with a variety of other side effects that may require additional treatment to correct. Rapid intravenous administration of high-dose loop diuretics should be avoided whenever possible, because hearing loss to the point of deafness can result from middle ear toxicity. Skin reactions from photosensitivity to rashes are not uncommon, and other hypersensitivity reactions including interstitial nephritis may occur. High doses of loop diuretics can worsen glucose tolerance and may result in hyperuricemia and symptoms of gout, prompted by increased uric acid reabsorption. Thiazide diuretics share most of the side effects seen with loop diuretics, although an association with pancreatitis appears be unique to loop diuretics.

Recommendation

7.27 Patients requiring diuretic therapy to treat fluid retention associated with HF generally require chronic treatment, although often at lower doses than those required initially to achieve diuresis. Decreasing or even discontinuing diuretics may be considered in patients experiencing significant improvement in clinical status and cardiac function or in those who successfully restrict dietary sodium intake. These patients may undergo cautious weaning of diuretic dose and frequency with careful observation for recurrent fluid retention. (Strength of Evidence = C)

Background

Reduced diuretic requirement is not uncommon during the course of HF treatment. The initiation of more effective therapies, such as ACE inhibitors and beta blockers, may result in substantial improvement in underlying LV dysfunction and in neurohormonal abnormalities that result in sodium and water retention. Improvement in adherence to dietary sodium restrictions is not unusual during chronic therapy for HF and may substantially reduce the need for diuretic therapy. Reevaluation of diuretic dose and frequency should occur over the course of initiation and titration of therapy.

Recommendation

7.28 It is recommended that patients and caregivers be given education that will enable them to demonstrate understanding of the early signs of fluid retention and the plan for initial therapy. (Strength of Evidence = C)

Selected patients may be educated to adjust daily dose of diuretic in response to weight gain from fluid overload (typically short-term weight gain of 2 to 4 lb). (Strength of Evidence = C) (See Section 6 for more information on this topic)

Background

Episodic increases in sodium intake over weeks and months of follow-up are expected, given the natural variation in diet common in the daily lives of patients with HF. If untreated, this excessive dietary sodium intake may result in development or recurrence of congestive symptoms. The ability to recognize early signs and symptoms of volume overload is an important aspect of self-care for these patients. Intervention early in the development of fluid overload may allow restoration of volume status without hospitalization.

A strategy effective in many patients involves adjustment of the diuretic dose according to increases in daily weight. Some patients find it effective to increase diuretic empirically when dietary sodium indiscretion occurs. In some patients with advanced HF, monitoring of renal function and potassium is necessary before or during these periods.

Digoxin

Recommendation

7.29 Digoxin may be considered to improve symptoms in patients with reduced LVEF (LVEF ≤40%) who have signs or symptoms of HF while receiving standard therapy, including ACE inhibitors and beta blockers:

- **NYHA class II-III (Strength of Evidence = B)**
- **NYHA class IV (Strength of Evidence = C)**

Background

Although little controversy exists as to the benefit of digoxin in patients with symptomatic HF with reduced LVEF

and concomitant atrial fibrillation, the debate continues over its current role in similar patients with normal sinus rhythm. Information regarding digoxin's mechanism of action and ongoing analyses of clinical data from the Digitalis Investigation Group (DIG) trial and the combined databases of several other large trials provide evidence of digoxin's efficacy.[93–99] Digoxin, a drug that is inexpensive and can be given once daily, represents the only oral agent with positive inotropic effects approved for the management of HF, although as discussed below, in the low doses currently used, digoxin may work more by neurohormonal modulation than inotropy. Digoxin has an important therapeutic role in symptomatic patients with HF from reduced LVEF.

The efficacy of digoxin in HF with reduced LVEF has traditionally been attributed to its relatively weak positive inotropic action arising from inhibition of sodium-potassium ATPase and the resulting increase in cardiac myocyte intracellular calcium. However, digitalis has additional actions that may contribute significantly to its beneficial effects in patients with HF. Digoxin has important neurohormonal modulating effects that cannot be ascribed to its inotropic action, and it ameliorates autonomic dysfunction as shown by studies of heart rate variability, which indicate increased parasympathetic and baroreceptor sensitivity during therapy.[100–103]

The DIG trial provides important data concerning the efficacy of digoxin in patients with HF from reduced LVEF.[97] In the main part of this trial, 6800 patients with LVEF ≤45% were randomized to digoxin or placebo in addition to diuretics and ACE inhibitors. The primary end point of all-cause mortality was not significantly different between the placebo and the digoxin groups. The need for hospitalization and cointervention (defined as increasing the dose of diuretics and ACE inhibitors or adding new therapies for worsening HF) was significantly lower in the digoxin group, even in those patients who were not previously taking digoxin. Twenty-eight percent fewer patients on digoxin compared with placebo were hospitalized for worsening HF. Digoxin has not been studied prospectively in patients on current neurohormonal blockade including both ACE-inhibitors and beta blockers, and retrospective studies suggest it may not provide benefit in these patients. A prospective, randomized trial evaluating the benefits of digoxin would be valuable.[104,105]

Results from the DIG study showed a neutral effect on the primary study endpoint, mortality from any cause, during an average follow-up of approximately 3 years. These long-term data are consistent with recent results obtained from an analysis of the combined Prospective Randomized Study of Ventricular Function and Efficacy of Digoxin (PROVED) and Randomized Assessment of Digoxin on Inhibitors of the Angiotensin Converting Enzyme) RADIANCE study databases.[99] In this analysis, patients who continued digoxin as part of triple therapy with diuretics and an ACE inhibitor were much less likely to develop worsening HF (4.7%) than those treated with a diuretic alone (39%, $P < .001$), diuretic plus digoxin (19%, $P = .009$), or diuretic plus an ACE inhibitor (25%, $P = .001$). The DIG trial was conducted prior to the widespread use of beta blockers, and no large trial of digoxin in addition to therapy with both ACE-inhibitors and beta blockers is available.

Although the number of patients in the DIG trial with NYHA functional class IV HF was limited, retrospective analysis of this subgroup found clear evidence of clinical benefit of digoxin.[106] Other results from this trial confirm that digoxin works to improve symptoms across the spectrum of HF with reduced LVEF. A prespecified subgroup analysis of patients with evidence of severe HF, as manifested by LVEF <25% or cardiothoracic ratio (CTR) >0.55, showed the benefit of digoxin.[100,106] The following reductions in the combined endpoint of all-cause mortality or hospitalization were seen on digoxin compared with placebo: 16% reduction (95% CI 7–24%) in patients with an LVEF <25%, and a 15% reduction (95% CI 6–23%) in patients with a CTR >0.55. Reductions in the risk of the combined endpoint of HF-related mortality or hospitalization were even more striking: 39% for patients with LVEF <25% and 35% for patients with a CTR >0.55.

Evidence for the efficacy of digoxin in patients with mild symptoms of HF has been provided by a second retrospective cohort analysis of the combined PROVED and RADIANCE databases.[107] The outcome of patients in these trials randomized to digoxin withdrawal or continuation was categorized using a prospectively obtained HF score based on clinical signs and symptoms. Patients in the mild HF group who were randomized to digoxin withdrawal were at increased risk of treatment failure and had deterioration of exercise capacity and LVEF compared with patients who continued digoxin (all $P < .01$).

Recommendation

7.30 It is recommended that the dose of digoxin, which should be based on lean body mass, renal function, and concomitant medications, should be 0.125 mg daily in the majority of patients and the serum digoxin level should be <1.0 ng/mL, generally 0.7-0.9 ng/mL. (Strength of Evidence = B)

Background

Recent data suggest that the target dose (and serum concentration) of digoxin therapy should be lower than traditionally assumed. Although higher doses may be necessary for maximal hemodynamic effects,[94] beneficial neurohormonal and functional effects appear to be achieved at relatively low serum digoxin concentrations (SDC) typically associated with daily doses of 0.125 to 0.25 mg.[94,103,108] A retrospective analysis of the relationship of SDC to outcomes in the DIG trial demonstrated a strong direct relationship between the risk of death and SDC, with concentrations >1.2 ng/mL being associated with harm, whereas concentrations <1.0 ng/mL were associated with

favorable outcomes.[109] These findings supporting the efficacy of low SDC are reinforced by a retrospective cohort analysis of the combined PROVED and RADIANCE databases indicating that patients with a low SDC (<0.9 ng/mL) were no more likely to experience worsening symptoms of HF on maintenance digoxin than those with a moderate (0.9−1.2 ng/mL) or high (>1.2 ng/mL) SDC.[93,109] All SDC groups were significantly less likely to deteriorate during follow-up compared with patients withdrawn from digoxin.

Therefore, patients with reduced LVEF and normal sinus rhythm should be started on a maintenance dose of digoxin (no loading dose) of 0.125 or 0.25 mg once daily based on ideal body weight, age, and renal function. For young patients with normal renal function, a dose of 0.25 mg/day will be typical. Most patients with HF are older and have reduced renal function and should begin at 0.125 mg daily. Patients with a baseline conduction abnormality, or who are small in stature or elderly, should be started at 0.125 mg/day, which can be up-titrated if necessary. Updated dosing nomograms have been published in light of the recognized benefits of digoxin at lower serum concentrations, and they may be useful to clinicians in selecting appropriate an appropriate digoxin dose.[110] After dosing has continued for a sufficient period for serum concentration to reach steady state (typically 5 daily doses), some clinicians consider the measurement of a SDC, especially in elderly patients or those with impaired renal function where the digoxin dose often is not predictive of SDC. SDC measurements may be considered when (1) a significant change in renal function occurs; (2) a potentially interacting drug (amiodarone, quinidine, verapamil, itraconazole, erythromycin, clarithromycin, ritonavir, propafenone, or cyclosporine, and others) is added or discontinued; or (3) confirmation of suspected digoxin toxicity is necessary in a patient with signs/symptoms or electrocardiogram changes consistent with this diagnosis. Samples for trough SDC should be drawn more than 6 hours after dosing; otherwise, the result is difficult to interpret because the drug may not be fully distributed into tissues.

Recommendations

7.31 Digoxin should be considered for achieving adequate control of the ventricular response to atrial fibrillation in patients with HF. (Strength of Evidence = B)

7.32 High doses of digoxin (maintenance dose >0.25 mg daily) for the purpose of rate control are not recommended. (Strength of Evidence = C)

Background

Adequate ventricular rate control is important in patients with atrial fibrillation. During chronic therapy, the recommendations followed in the Atrial Fibrillation Follow-up Investigation of Sinus Rhythm Management (AFFIRM) trial are a reasonable starting point.[111] These recommendations include: a resting heart rate ≤80 bpm, an average heart rate by Holter monitor of ≤100 bpm, and no heart rate >110% of the age-predicated maximum or a heart rate ≤110 bpm during a 6-minute walk test. Digoxin alone is often inadequate to control ventricular response in patients with atrial fibrillation. Digoxin slows ventricular response to atrial fibrillation through enhancement of vagal tone. However, with exertion or other increases in sympathetic activity, vagal tone may diminish and ventricular rate accelerate. Addition of a beta blocker complements the pharmacologic action of digoxin and improves rate control. When beta-adrenergic blockers cannot be used, amiodarone has been used by some physicians, but chronic use has potentially significant risks, including thyroid disease and lung toxicity. If amiodarone is added, the dose of digoxin should be reduced by half and the SDC should be monitored to maintain the serum concentration in the desired range. Short-term, intravenous administration of diltiazem or amiodarone has been used for the acute treatment of patients with very rapid ventricular response, especially if the rapid rate is felt to be contributing to hemodynamic compromise. The negative inotropic effects of nondihydropyridine calcium channel blockers (diltiazem and verapamil) must be considered if these agents are used. Digoxin does not lower blood pressure; thus, it may be particularly valuable when hypotension from other agents is a concern.

Although digoxin continues to play a role in some patients with HF and atrial fibrillation, the traditional practice of arbitrarily increasing the dose and SDC of digoxin until ventricular response is controlled should be abandoned, because the risk of digoxin toxicity increases as well.

Anticoagulation and Antiplatelet Drugs

Recommendation

7.33 Treatment with warfarin (goal international normalized ratio [INR] 2.0-3.0) is recommended for all patients with HF and chronic or documented paroxysmal, persistent, or long-standing atrial fibrillation (Strength of Evidence = A) or a history of systemic or pulmonary emboli, including stroke or transient ischemic attack (Strength of Evidence = C), unless contraindicated.

Background

Patients with HF are recognized to be at increased risk for arterial or venous thromboembolic events. In addition to atrial fibrillation and poor ventricular function, which promote stasis and increase the risk of thrombus formation, patients with HF have other manifestations of hypercoagulability. Evidence of heightened platelet activation, increased plasma and blood viscosity, and increased plasma levels of fibrinopeptide A, beta-thromboglobulin, D-dimer, and von Willebrand factor have been found in many patients.[112−114] Despite a predisposition, estimates

regarding the incidence of thromboemboli in patients with HF vary substantially between 1.4% and 4.2% per 100 patient years.[115–117] Although variability in the reported incidence likely results from differences in the populations studied and the methodology used to identify these events, the consensus is that pulmonary and systemic emboli are not common in HF patients in sinus rhythm. Traditionally, discussion of anticoagulation in patients with HF has centered on warfarin. Antiplatelet agents are often used in patients with HF from ischemic heart disease.

Previous guidelines have recommended warfarin anticoagulation in patients with HF complicated by atrial fibrillation or prior thromboembolic events.[118] Warfarin anticoagulation was specifically not recommended in patients with HF in the absence of these indications.

Recommendations regarding warfarin use, in the absence of atrial fibrillation or clinically overt systemic or pulmonary thromboemboli, must be made on the basis of cohort data and expert opinion. The likely incidence of thromboembolic events and the possibility of averting them with warfarin are important considerations for any guideline recommendation. In addition, the potential beneficial effects of warfarin on coronary thrombotic events, independent of embolic phenomena, must be taken into account. The substantial clinical trial data reflecting the beneficial effects of antiplatelet therapy in patients with ischemic heart disease suggest that the role of this therapy in patients with reduced LVEF should be addressed.

Previous guideline recommendations have been positive concerning warfarin therapy in patients with HF complicated by atrial fibrillation, a common clinical presentation. The benefit of warfarin anticoagulation in this setting is well established through several randomized trials.[119] Warfarin anticoagulation should be implemented in these patients unless clear contraindications exist.

Recommendation

7.34 It is recommended that patients with symptomatic or asymptomatic ischemic cardiomyopathy and documented recent large anterior MI or recent MI with documented LV thrombus be treated with warfarin (goal INR 2.0-3.0) for the initial 3 months post-MI (Strength of Evidence = B) unless contraindicated.

Other patients with ischemic or nonischemic cardiomyopathy and LV thrombus should be considered for chronic anticoagulation, depending on the characteristics of the thrombus, such as its size, mobility, and degree of calcification. (Strength of Evidence = C)

Background

LV thrombus is a frequent finding in patients with dilated dysfunctional ventricles, especially in patients who have suffered a large anterior MI, although the incidence appears to be declining with modern therapies.[120–122] LV thrombus is associated with thromboembolism, especially cerebral embolism.[123–125] Two-thirds of these embolic events occur in the first week after MI.[124,125] When LV mural thrombus is present, anticoagulation does appear to reduce the incidence of subsequent embolic events.[123] There are no randomized trials of anticoagulation for LV thrombus, but the data presented have led to a recommendation for short-term (3 months) anticoagulation in patients with a large anterior MI and wall motion abnormality or in patients with LV thrombus.[126]

Background

Cohort analyses examining the relationship between warfarin use and noncoronary thromboembolism in patients with HF have not yielded consistently positive findings.[115,117,127–130] It is possible that the lack of consistent benefit was related to the low incidence of identifiable embolic events in these populations. Other retrospective evaluations of the use of anticoagulation in patients with HF have also yielded conflicting results.[131–133] Thromboembolic events were not different in HF patients who were taking warfarin as compared to those who were not in several retrospective analyses.[117,134,135] Warfarin was associated with a reduction in cardiovascular events and death in a retrospective analysis of the Studies of Left Ventricular Dysfunction (SOLVD) studies,[136] whereas no difference in antiplatelet or anticoagulant therapy were observed in another analysis.[137]

A recent review suggested that anticoagulation with warfarin in patients with HF reduced death and cardiovascular events but that the data were insufficient to recommend routine use.[138] Two prospective randomized trials of anticoagulation have been published since that review but both were underpowered. The Warfarin/Aspirin Study in Heart Failure (WASH) randomized 279 patients with HF to warfarin (INR target 2.5), 300 mg aspirin, or no treatment.[139] There were no differences in the combined primary outcomes of death, MI, or stroke. However, significantly more patients randomized to aspirin were hospitalized for ADHF or serious adverse gastrointestinal events.

In the Warfarin and Antiplatelet Therapy in Chronic Heart Failure (WATCH) trial, patients with symptomatic HF and reduced LVEF were randomized to aspirin 162 mg/day, clopidogrel 75 mg/day, or open-label warfarin to achieve an INR of 2.5 to 3.[140] The primary endpoint of the study was the composite of all-cause mortality, nonfatal MI, and non-fatal stroke. The majority of patients had an ischemic etiology of HF, although the study population was not limited to patients with coronary artery disease. There were no statistically significant differences in the primary endpoint for warfarin versus aspirin, for clopidogrel versus aspirin, or for warfarin versus clopidogrel.[140] However, as in WASH, fewer patients randomized to warfarin were hospitalized for HF. A recent retrospective

analysis of 290 patients with HF and LVEF <35% and idiopathic dilated cardiomyopathy reported an odds ratio of 3.4 (P = .027) for stroke in those with LV thrombus but no difference in mortality.[141] In the absence of strong data, the decision to anticoagulate must be an individual one. There are insufficient data for or against the use of warfarin in patients with dilated cardiomyopathy and LVEF ≤35%.

The analysis of the SOLVD population mentioned above focused on the relation between warfarin use and the risk of all-cause mortality rather than risk for embolic events.[136] After adjustment for baseline differences, patients treated with warfarin at baseline had a 24% lower risk of mortality during follow-up. Warfarin use also was associated with an 18% reduction in the combined endpoint of death or hospitalization for HF. In the SOLVD population, the benefit associated with warfarin use was not significantly influenced by (1) presence or absence of symptoms, (2) randomization to enalapril or placebo, (3) gender, (4) presence or absence of atrial fibrillation, (5) age, (6) LVEF, (7) NYHA class, or (8) etiology.

The benefit associated with warfarin use in the cohort analysis of the SOLVD population was related to a reduction in cardiac mortality. Specifically, there was a significant reduction among warfarin users in deaths that were identified as sudden, in deaths associated with HF, and in fatal MI There was no significant difference in deaths considered cardiovascular but non-cardiac, including pulmonary embolism and fatal stroke. Some caution is needed related to this finding as the number of cardiovascular deaths that were non-cardiac was far smaller than the number of cardiac deaths.

Reduction in ischemic events is one potential explanation for the apparent benefit from warfarin in the SOLVD study. Warfarin users showed a reduced rate of hospitalization for unstable angina or nonfatal MI. Prior investigations in patients following acute MI showed that warfarin anticoagulation, when begun within 4 weeks, reduced the incidence of fatal and non-fatal coronary events, as well as pulmonary emboli and strokes.[139]

As with other post-hoc cohort analyses, it is possible that the findings from the SOLVD study may result from unidentified differences between the treatment groups, for which statistical correction could not adequately adjust. For this reason, evidence from any cohort study must be considered less powerful than that derived from randomized, controlled trials.

Recommendations

7.35 Long-term treatment with an antiplatelet agent, generally aspirin in doses of 75 to 81 mg, is recommended for patients with HF due to ischemic cardiomyopathy, whether or not they are receiving ACE inhibitors. (Strength of Evidence = B)

Warfarin (goal INR 2.0-3.0) and clopidogrel (75 mg) also have prevented vascular events in post-MI patients and may be considered as alternatives to aspirin. (Strength of Evidence = B)

7.36 Routine use of aspirin is not recommended in patients with HF without atherosclerotic vascular disease. (Strength of Evidence = C)

Background

Combined Use of Aspirin and an ACE Inhibitor. Strong evidence supports the clinical benefit of both aspirin and ACE inhibitors in ischemic heart disease and atherosclerosis.[142-145] However, post-hoc analyses of large randomized trials involving ACE inhibitors in HF and post-MI have raised the possibility of an adverse drug interaction between aspirin and ACE inhibitors.[146]

It is critical to understand the possible nature of the adverse interaction raised by these retrospective analyses. Because both aspirin and ACE inhibitors are beneficial in ischemic heart disease, patients taking both agents might be expected to do better than patients on either agent alone. However, if the 2 drugs have similar mechanisms of action, then additive benefit would not be expected. Another possibility is that one drug might antagonize the effects of the other, resulting in reduced benefit from the combination.

Post-MI. Early work concerning the nature of the interaction in ischemic heart disease, using data from the Cooperative New Scandinavian Enalapril Survival Study II (CONSENSUS II) and the Global Utilization of Streptokinase and Tissue Plasminogen Activator for Occluded Coronary Arteries (GUSTO-1) studies in post-MI patients, suggested not only lack of additive benefit, but also the possibility of a negative effect on mortality from the combination of aspirin and ACE inhibition. A large-scale meta-analysis of patients after acute MI failed to confirm an adverse interaction, with evidence of significant benefit from ACE inhibition in patients taking and not taking aspirin.[147] However, the point estimate for the reduction in mortality in patients taking the combination of aspirin and ACE inhibition, whereas not statistically less than for aspirin alone, was lower, providing no support for additive benefit from the 2 drugs.

Heart Failure. A retrospective cohort analysis of the SOLVD study found that patients on antiplatelet therapy (assumed to be aspirin in the great majority of cases) derived no additional survival benefit from the addition of enalapril.[146] Other studies have shown no clear evidence of harm from the combination of aspirin and ACE inhibitors in patients with HF.[148]

Relationship to Dose. There is also some evidence that the potential interaction between aspirin and ACE inhibitor may be dose-related. A meta-analysis of all hypertension and HF patients who have received both aspirin and ACE inhibitors suggests that aspirin at doses ≤100 mg did not interact with ACE inhibitors.[149] Any interaction, if

observed, occurred at higher doses of aspirin. A more recent meta-analysis could not confirm or exclude a modest effect of aspirin on the benefits of ACE inhibitors.[147]

A potential mechanism for the hypothesized adverse interaction between aspirin and ACE inhibitors in patients with HF involves prostaglandin synthesis. ACE inhibition is felt to augment bradykinin, which in turn stimulates the synthesis of various prostaglandins that may contribute vasodilatory and other salutary effects. In the presence of aspirin, the bradykinin-induced increase in prostaglandins should be attenuated or blocked, potentially reducing the benefits of ACE inhibition. Invasive hemodynamic monitoring has demonstrated that the acute hemodynamic effect of enalapril is blunted by concomitant administration of aspirin.[150] Another possibility is that aspirin and ACE inhibitors act in a similar fashion in HF so that no added benefit is gained from the combination. ACE inhibitors appear to reduce ischemic events in HF patients possibly through antithrombotic effects, which could mimic those of antiplatelet agents. Recent study results suggesting that aspirin may have independent beneficial action on ventricular remodeling support the hypothesis of similar mechanisms of action for ACE inhibitors and aspirin.[151]

Development of the adenosine diphosphate antagonists, ticlopidine and clopidogrel, provide alternative therapy for platelet inhibition that does not appear to influence prostaglandin synthesis.[152] In direct comparison with aspirin, large-scale clinical trial results have established the efficacy of clopidogrel in the prevention of vascular events in patients with arteriosclerotic disease.[153] In WATCH, there were no statistically significant differences in death, MI, or stroke for warfarin versus aspirin, for clopidogrel versus aspirin, or for warfarin versus clopidogrel.[140] A hemodynamic study found a similar reduction in systemic vascular resistance in HF patients treated with the combination of ACE inhibitor and ticlopidine versus ACE inhibitor alone, suggesting no adverse hemodynamic interaction between ACE inhibition and this type of antiplatelet compound.[154] Definitive resolution of the therapeutic implications of the aspirin-ACE inhibitor interaction and determination of alternative therapy, if any, in HF awaits the results of additional studies.

Amiodarone Therapy

Recommendation

7.37 Antiarrhythmic agents, including amiodarone, are not recommended for the primary prevention of sudden death in patients with HF. (Strength of Evidence = A)

Background

Ventricular arrhythmias are common in HF patients, and sudden cardiac death continues to account for a significant proportion of the mortality in this syndrome. Sudden death in HF may arise from a variety of causes, including bradyarrhythmias, conduction disturbances, electromechanical dissociation, acute MI, or pulmonary embolus. However, the majority of these deaths are thought to be due to ventricular tachyarrhythmias. Therefore, there has been considerable interest in the potential role of antiarrhythmic drug therapy in patients with HF.[155] Randomized, placebo controlled trials of antiarrhythmic drug therapy for ventricular arrhythmias or atrial fibrillation has not been shown to improve survival in HF.[5,155–157] The frequency of ambient ventricular ectopic activity is a marker for disease severity. Suppression of ventricular ectopy with amiodarone does not improve survival.[155,157] Many antiarrhythmic drugs have adverse hemodynamic effects sufficient to have negative consequences in patients with HF. Patients with HF are at higher risk for proarrhythmic effects of antiarrhythmic agents. The major role for the use of these agents in HF is to reduce recurrences of symptomatic arrhythmias, usually in patients who have an implanted cardioverter defibrillator (ICD).[158]

Amiodarone blocks multiple cardiac ionic currents and has activity against ventricular and atrial arrhythmias, as well as slowing the sinus rate and the ventricular response to atrial fibrillation. Bradycardia is the major proarrhythmic effect, but the potential for multiple noncardiac toxicities (pulmonary, thyroid, liver, neurologic) require ongoing monitoring, and multiple potential drug interactions often require consideration. Amiodarone therapy has not been shown to improve mortality in randomized placebo controlled trials.[155,157] The Sudden Cardiac Death in Heart Failure Trial (SCD-HeFT) tested the hypothesis that either amiodarone or an ICD, or both, improve survival compared with placebo in patients with NYHA Class II or III HF and LVEF $<35\%$ of ischemic or nonischemic etiology.[155] A total of 2521 patients were randomly assigned to ICD, amiodarone, or placebo. The patients were well treated: 87% were on ACE inhibitors or ARBs and 78% were on beta blockers at last follow-up. ICD, but not amiodarone improved mortality compared to placebo (Section 9).

Amiodarone was compared to placebo in a smaller double-blind, randomized trial that enrolled 674 patients with a mean age of 66 years. The majority (56%) had NYHA class II symptoms, and their mean LVEF = 26%.[157] No differences were observed in all-cause or cardiac mortality or sudden death rates between the amiodarone and placebo groups. Another small randomized trial did suggest a beneficial effect of amiodarone, but there were significant limitations in the design and conduct of this trial. Treatment assignment was randomized, but not double-blind or placebo-controlled. The trial was discontinued prematurely when a 28% reduction was observed in all-cause mortality, the primary endpoint. Although not strictly involving HF patients, 2 post-MI trials found no benefit of amiodarone on mortality.[159,160]

A retrospective analysis of the COMET trial evaluated mortality among patients receiving amiodarone at baseline.[161] Patients who were treated with amiodarone at baseline had a higher risk of death due to circulatory failure

during follow-up than those who did not receive amiodarone, irrespective of functional class (HR 2.4, 95% CI 1.9−3.1, $P < .001$). Amiodarone was not associated with an increased risk of sudden death in this analysis.[161]

Amiodarone has significant long term toxicities, including lung, liver, and thyroid toxicity such that periodic monitoring is required during long term therapy. The most common cardiac adverse effect is bradycardia which can be potentiated by beta-adrenergic blockers. Bradycardia may also increase RV pacing from defibrillators which may have an adverse hemodynamic effect in some patients. Whether these effects contributed to the increased mortality observed in the subgroup of patients with more severe (NYHA Class III) HF in SCD-HeFT is not known.

Therapy with Vaughn Williams Class I drugs (quinidine, disopyramide, mexiletine, flecainide, propafenone) should be avoided. Flecainide has been shown to increase mortality when administered to patients with prior MI.[162] These agents have been linked to increased mortality in HF patients with atrial fibrillation.[163] Potential adverse effects can include a negative inotropic effect of sodium channel blockade and proarrhythmic effects. The Class III potassium channel blocking agents sotalol and dofetilide have not been shown to improve mortality in HF and are associated with a risk of proarrhythmia (most often the polymorphic ventricular tachycardia torsade de pointes, associated with QT prolongation). Impaired renal function that reduces excretion of these drugs and diuretic induced hypokalemia increase the proarrhythmia risk. The d-isomer of sotalol (d-sotalol) increased mortality in survivors of MI.[164] A randomized trial of dofetilide in patients with ventricular dysfunction found no benefit on mortality, although hospitalizations were reduced, possibly due to decreased atrial fibrillation.[165] A significant incidence of torsade de points was noted, despite precautions to exclude patients with renal insufficiency and other risk factors for QT prolongation.

Dronedarone blocks multiple cardiac ionic currents, and it has been shown to have activity to reduce atrial fibrillation and to reduce the ventricular response in atrial fibrillation when it recurs. Efficacy appears to be less than for amiodarone.[166] It reduces tubular secretion of creatinine, increasing serum creatinine. A study in patients with HF and LVEF <35% was terminated early due to an two fold increased mortality in patients treated with dronedarone.[167] The FDA approval states that dronedarone is contraindicated in patients with Class IV HF or those with Class II or III HF who have had a recent HF decompensation.

Recommendations

7.38 In patients with HF and an ICD, amiodarone may be considered to reduce the frequency of recurrent symptomatic arrhythmias causing ICD shocks. (Strength of Evidence = C)

7.39 It is recommended that when amiodarone therapy is initiated, the potential for interactions with other drugs be reviewed. The maintenance doses of digoxin, warfarin, and some statins should be reduced when amiodarone is initiated and then carefully monitored. Adjustment in doses of these drugs and laboratory assessment of drug activity or serum concentration after initiation of amiodarone is recommended. (Strength of Evidence = A)

7.40 Routine use of amiodarone therapy for asymptomatic arrhythmias that are not felt to contribute to HF or ventricular dysfunction is not recommended. (Strength of Evidence = B)

Background

Amiodarone therapy modifies the pharmacokinetics of a number of drugs commonly used in patients with HF. In particular, it may substantially enhance the actions of digoxin and warfarin, with the definite potential of adverse clinical consequences. In general, the digoxin dose should be reduced by half, but follow-up determination of SDC is desirable to ensure a concentration of 0.5-0.9 ng/mL. The warfarin dose should be adjusted to maintain the INR target for the individual patient. Even after amiodarone is discontinued, these pharmacokinetic interactions can persist for months due to its long half-life. Since amiodarone also has beta-blocking properties, substantial bradycardia may occur with this combination of drugs. Amiodarone is not recommended for asymptomatic arrhythmias or those not causing HF due to the multiple drug-drug interactions and the serious side effect profile.

Polyunsaturated Fatty Acids

Recommendation

7.41 n-3 polyunsaturated fatty acids (PUFA) may be considered to reduce mortality in HF patients with NYHA class II-IV symptoms and reduced LVEF. (Strength of Evidence = B)

Background

n-3 polyunsaturated fatty acids (PUFA) have been associated with lower mortality after MI, primarily from a reduction in sudden cardiac death.[168] In the GISSI-Prevenzione trial, 3-year treatment with low-dose n-3 PUFA was associated with a significant reduction of total mortality (21%) in patients who survived a recent MI. In the published design paper for the subsequent GISSI-HF trial, the authors described the results of an unpublished, post-hoc analysis of the GISSI-Prevenzione trial, showing that in nearly 2000 post-infarction patients with LV dysfunction enrolled in the trial, the effects of n-3 PUFA on all-cause and sudden mortality were similar to those observed in the overall trial population.[169] A single randomized controlled trial, the Italian GISSI-HF trial, has been conducted with n-3 PUFA in the HF population.[170] Patients with NYHA Class II−IV symptoms and LVEF <40% were

enrolled. Patients with LVEF ≥40% were also eligible, provided they had been hospitalized for HF at least once in the preceding year (accounted for 9% of the total population). Patients were randomized to either 1 g/day of PUFA (850−882 mg eicosapentaenoic acid and docosahexaenoic acid as ethyl esters in the average ratio of 1:1.2) or matching placebo. The primary endpoints were time to death, and time to death or cardiovascular hospitalization. A total of 3494 patients were enrolled in the n-3 PUFA group and 3481 in the placebo group. All cause mortality was 27% in the n-3 PUFA group and 29% in the placebo group (adjusted HR 0.91, 95.5% CI 0.833−0.998, $P=0.041$). All-cause death or cardiovascular hospitalization occurred in 57% of the n-3 PUFA treated patients and 59% of the placebo group (adjusted HR 0.92, 99% CI 0.849−0.999, $P=0.009$). Patients were receiving standard medical therapy for HF, with 93% on ACE-inhibitors or ARBs, 65% on beta blockers, and approximately 40% on spironolactone. N-3 PUFA was generally well tolerated, with gastrointestinal complaints being the most commonly reported adverse effect in both groups.[170] The therapy is not widely adopted, but it may be considered as an adjunctive therapy in patients with chronic HF.

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Section 8: Disease Management, Advance Directives, and End-of-Life Care in Heart Failure

Education and Counseling

Overview

The majority of heart failure (HF) care is performed at home by the patient and family or caregiver. If these individuals do not know what is required, fail to see its importance, or face barriers to engagement in self-care, they will not participate effectively. For this reason, comprehensive education and counseling are the foundation for all HF management. The goals of education and counseling are to help patients, their families, and caregivers acquire the knowledge, skills, strategies, problem solving abilities, and motivation necessary for adherence to the treatment plan and effective participation in self-care. The inclusion of family members and other caregivers is especially important, because HF patients often suffer from cognitive impairment, functional disabilities, multiple comorbidities and other conditions that limit their ability to fully comprehend, appreciate, or enact what they learn.[1–7]

Recommendation

8.1 It is recommended that patients with HF and their family members or caregivers receive individualized education and counseling that emphasizes self-care. This education and counseling should be delivered by providers using a team approach in which nurses with expertise in HF management provide the majority of education and counseling, supplemented by physician input and, when available and needed, input from dietitians, pharmacists, and other health care providers. (Strength of Evidence = B)

Teaching is not sufficient without skill building and specification of critical target behaviors. It is recommended that essential elements of patient education (with associated skills) are utilized to promote self-care as shown in Table 8.1. (Strength of Evidence = B)

Background

Self Care. Self-care describes the process whereby a patient participates actively in the management of his or her HF, usually with the help of a family member or caregiver. Self-care includes both maintenance and management.[8,9] Self-care maintenance refers to healthy life-style choices (eg, exercising, maintaining a normal body weight) and treatment adherence behaviors (eg, monitoring weight changes, limiting dietary sodium, taking medications, getting routine immunizations). Self-care management is a cognitive process that includes recognizing signs and symptoms, evaluating their importance, implementing a self-care treatment strategy (eg, diuretic administration), and evaluating its effectiveness. Self-efficacy, or confidence in ones ability to perform self-care, has been shown to influence self-care management abilities.[10]

Lack of knowledge and patient or caregiver misconceptions about how to participate in HF care is common.[1,4,11–17] The end result is non-adherence. HF patients, their families, and caregivers undertake the many behaviors involved in the care of HF in settings far removed from oversight by a health care provider. Teaching that emphasizes self-care is therefore a critical component of HF disease management programs.[18]

Knowledge alone is insufficient to promote adherence and effective self-care. An essential adjunct is skill building with target behaviors.[14] Skills needed include the ability to read food labels, adapt preferred foods to low-sodium versions, select low-sodium foods in the grocery store, prepare

Table 8.1. Essential Elements of Patient Education With Associated Skills and Target Behaviors

Elements of Education	Skill Building and Critical Target Behaviors
Definition of HF (linking disease, symptoms, and treatment) and cause of patient's HF	• Discuss basic HF information, cause of patient's HF, and how symptoms relate to HF status
Recognition of escalating symptoms and concrete plan for response to particular symptoms	• Identify specific signs and symptoms (eg, increasing fatigue or shortness of breath with usual activities, dyspnea at rest, nocturnal dyspnea or orthopnea, edema) • Perform daily weights and know how to respond to evidence of volume overload • Develop action plan for how and when to notify the provider, changes to make in diet, fluid and diuretics
Indications and use of each medication	• Reiterate medication dosing schedule, basic reason for specific medications, and what to do if a dose is missed
Modify risks for HF progression	• Smoking cessation • Maintain blood pressure in target range • Maintain normal HgA1c, if diabetic • Maintain specific body weight
Specific diet recommendations: individualized low-sodium diet; recommendation for alcohol intake	• Understand and comply with sodium restriction • Demonstrate how to read a food label to check sodium amount per serving and sort foods into high- and low-sodium groups • Reiterate limits for alcohol consumption or need for abstinence if history of alcohol abuse
Specific activity/exercise recommendations	• Comply with prescribed exercise
Importance of treatment adherence and behavioral strategies to promote	• Plan and use a medication system that promotes routine adherence • Plan for refills

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palatable food with little or no added sodium, track sodium intake, and choose a low-sodium meal in a restaurant. Patients need guidance to develop an individualized system for medication adherence. Symptom management skills include the ability to monitor for and recognize a significant change in signs or symptoms and select an appropriate treatment strategy. Many HF programs advocate a self-directed diuretic scheme for managing significant increases in body weight.[19,20]

Recommendation

8.2 It is recommended that patients' literacy, cognitive status, psychological state, culture, and access to social and financial resources be taken into account for optimal education and counseling. Because cognitive impairment and depression are common in HF and can seriously interfere with learning, patients should be screened for these. Patients found to be cognitively impaired need additional support to manage their HF. (Strength of Evidence = B)

Background

A number of physical, cognitive, social, emotional, and environmental factors can affect an individual's learning ability and should be taken into account when planning education and counseling.[1,4,6] Patients often are not adept at communicating potential problems to their health care providers, who therefore must actively assess for them.

At least 20% of adults in the United States (US) cannot read at a fourth- or fifth-grade level.[21] Low literacy has been shown to be a major barrier to learning about illness.[22] Many patients in the US do not speak or read English.[23] Illiteracy and language barriers can be improved by including family members and caregivers in counseling; by using a variety of teaching methods, such as video and group discussion; by translating teaching materials; and by carefully constructing teaching materials at an accessible reading level, usually fifth or sixth grade.

Health literacy, a related but different concept, is also a major problem for patients with HF. Health literacy refers to an individual's ability to understand and act upon health information. In a national survey, only 12% of American adults were considered proficient in health literacy; 22% of adults' health literacy was considered basic, indicating they were able to read simply worded material and solve one-step problems; while another 14% of adults had less than basic health literacy, meaning they had difficulty comprehending even simple instructions.[24] Low health literacy is associated with decreased knowledge of one's medical condition,[22,25–29] poor medication recall,[30] non-adherence to treatment plans,[26,28] poor self-care behaviors,[22,28,31] compromised physical and mental health,[32,33] greater risk of hospitalization,[34,35] and increased mortality.[36,37]

Although the literature specifically addressing issues of low health literacy in patients with HF is limited, it is consistent with the larger body of health literacy literature.[38–41] In one study, 38% of patients could not read and understand their own medication bottle labels, and this poor health literacy was associated with increased emergency department use for cardiac related problems.[42] To ensure appropriate patient engagement in self-care, it is essential that clinicians treating patients with HF address low literacy by identifying patients at risk, documenting learning preferences, using appropriate teaching materials, and stressing effective communication.

Cognitive impairment is probably more prevalent than recognized in HF patients [43–47] and can seriously affect patients' ability to learn and retain information. Rates of cognitive impairment between 23% and 53% have been documented in community-dwelling elders with HF.[43–46] Depression is common in patients with HF, it is a significant predictor of mortality,[48–64] and it interferes with learning and successful adjustment to HF.[65] HF patients should be routinely screened for depression. (See Section 6, Nonpharmacologic Therapy, for screening guidelines and treatment recommendations).

Although depression is associated with poorer outcomes in HF patients, the treatment of depression has not been demonstrated to improve outcomes.[66] Patients with cognitive impairment or depression need the support and assistance of a family member or caregiver. Home health nurses are recommended to assess and assist patients who lack a caregiver. Such patients can benefit from more intensive physician or nurse monitoring.

To screen for depression, a standardized instrument such as the Patient Health Questionnaire-2 score,[67] Beck Depression Inventory,[68] DISH,[69,70] or STOP-D questionnaire[71] can be used. Asking patients to read and interpret the instructions from a prescription medication bottle or procedure preparation instructions provides a good literacy assessment.

Recommendation

8.3 It is recommended that educational sessions begin with an assessment of current HF knowledge, issues about which the patient wants to learn, and the patient's perceived barriers to change. Education sessions should address specific issues (eg, medication nonadherence) and their causes (eg, lack of knowledge vs cost vs forgetting) and employ strategies that promote behavior change, including motivational approaches. (Strength of Evidence = B)

Background

Effective education and counseling is individualized to what the patient needs and wants to learn, builds on prior knowledge and experience, involves the patient in discussion and skill practice, and provides feedback and reinforcement.[72,73] A major difference between patient teaching and formal didactic education is that patient

teaching focuses on what patients need to *do* rather than what they need to *know*.[15]

Barriers to Change. HF patients often face barriers when they try to implement recommended behaviors. For example, a lack of social support compromises patient self-care.[74] Barriers to medication adherence include medication cost, cost of transportation to the pharmacy and clinic, confusion caused by prescriptions from multiple providers, and pharmacies in unsafe neighborhoods.[16,75] Other adherence barriers include medication unpleasantness, difficulty remembering, having to take too many medications each day, restrictions on travel, forgetting, and night-time awakening to urinate.[76] Barriers to sodium restriction adherence include time, cost, taste, difficulty understanding the diet, significant others not eating low-sodium food, interference with social obligations, confusion with dietary restrictions from other comorbid conditions, limitations on eating out, and difficulty modifying diet habits.[75–77] A common misunderstanding among HF patients is that an increase in fluid intake is necessary to compensate for excess urination.[15,77]

Readiness to Change. Optimal patient education is more than imparting information. Counseling emphasizes individualized delivery of important information, taking into account factors that interfere with successful participation in care, as well as a patient's readiness to change. Many patients are not ready to engage in the recommended behaviors. According to one model, those in *precontemplation* are not considering change, those in *contemplation* are thinking about change but have yet to make a commitment, and those in *preparation* are planning to change in the future and may have already engaged in some early steps of change.[78] Few patients are in the *action* (change has occurred) or *maintenance* (change has been maintained for 6 months or more) phases of change, even when the need for behavioral change was stressed by previous counseling. Increasing motivation may be very effective in moving patients from an early stage to an active stage of change.

Internal Motivation. Motivation is an important contributor to successful self-care. Motivational techniques are extremely effective for individuals in the early stages of change. Motivation interviewing, a technique that helps the patient resolve ambivalence regarding change, is effective even in those facing difficult tasks, such as abstinence from drinking or weight loss.[79,80] Cognitive-behavioral techniques, which emphasize modifying barriers to change, are also quite useful with patients in the early stages of change.[81] Specific techniques have been suggested for moving patients forward in each of the stages of change.[82] For example, patients considering change need information. On the other hand, information is often irritating to individuals in the contemplation stages of change, who might respond to an emphasis on the benefits to be derived from change. Those in the preparation stage benefit from comments that build confidence in their ability to make the necessary change or by suggestions that decrease perceived barriers.

Educational Techniques to Avoid. Fear and coercion are ineffective motivators because people who are pushed in one direction will resist change, even if the advocated approach is logical.[80,82] Paternalism, characterized by making decisions for or dictating decisions to patients, is rarely effective in the long-term because of lack of ownership by the patient over the decision.

Recommendation

8.4 It is recommended that the frequency and intensity of patient education and counseling vary according to the stage of illness. Patients in advanced HF or with persistent difficulty adhering to the recommended regimen require the most education and counseling. Patients should be offered a variety of options for learning about HF according to their individual preferences:

- **Videotape**
- **One-on-one or group discussion**
- **Reading materials, translators, telephone calls, mailed information**
- **Internet**
- **Visits**

Repeated exposure to material is recommended because a single session is never sufficient. (Strength of Evidence = B)

Background

Not all patients with HF have the same learning needs. Although one might argue that every patient could benefit from intensive education and counseling, current evidence suggests that those patients with few symptoms and less complicated HF may have worse outcomes in terms of health care resource use, costs, and quality of life when they receive intensive counseling.[83] Patients with more severe HF incur substantial benefit from an intensive intervention. Although most clinicians would argue for the value of face-to-face education and counseling, studies have shown that select patients who are motivated to learn and change can derive significant benefit from interventions delivered by mail, telephone, or technology.[84–86] These techniques are not likely to be successful with patients who suffer even mild cognitive impairment or have depressive symptoms, nor are they adequate for those with low literacy or low health literacy, poor social support, multiple comorbidities, or functional impairment. Regardless of the method used, it is imperative that information be covered more than once. Use of different methods may improve efficiency (eg, supplementing verbal with written materials).

Recommendation

8.5 It is recommended that during the care process patients be asked to:
- **Demonstrate knowledge of the name, dose, and purpose of each medication**
- **Sort foods into high- and low-sodium categories**
- **Demonstrate their preferred method for tracking medication dosing**
- **Show provider daily weight log**
- **Reiterate symptoms of worsening HF**
- **Reiterate when to call the provider because of specific symptoms or weight changes (Strength of Evidence = B)**

Background

Successful education is an interactive process in which patients and caregivers participate by asking questions and by demonstrating that they have comprehended and retained what they were told. Misperceptions by patients and family are very common, but they can be avoided when an interactive learning process is used.[4] Very few clinicians have strategies in place for assessing that patients have understood and retained the education given to them. Retention of learned material is poor among the elderly and any patient with a chronic disease, but it is enhanced when the learner shows mastery of the learned material by recitation of specific details or by demonstration.

Recommendation

8.6 During acute care hospitalization, only essential education is recommended, with the goal of assisting patients to understand HF, the goals of its treatment, and the post-hospitalization medication and follow-up regimen. Education begun during hospitalization should be supplemented and reinforced within 1–2 weeks after discharge, continued for 3–6 months, and reassessed periodically. (Strength of Evidence = B)

Background

The hospital is arguably the most difficult setting for patient and family education because patients are ill, anxious, and in circumstances that do not promote retention.[13,87] By many estimates, patients retain only a minority of information taught to them in the hospital.[10] One study showed that 46% of patients were noncompliant with their recently prescribed regimen and most demonstrated inadequate medication-related knowledge just 1 week after discharge, even when they received medication teaching.[16] In another study, half of all patients interviewed claimed they received no medication education before discharge, 70% claimed they received no written materials, only 43% of patients could name their discharge medications, and none could name even one side effect of their prescribed medications, regardless of whether or not they reported receiving information from a clinician.[88] Further, there was little agreement between patients and their physicians as to whether or not they had or had not received medication education from the physician.

Patient and caregiver knowledge about their HF and medication regimen must be confirmed by responses. Education should be reinforced and additional teaching started within 1 week of discharge.[89] Systematic education and counseling should continue for 3 to 6 months according to the needs of the patient and family or caregiver.[90]

The difficult circumstances under which discharge education is provided do not diminish its importance. One randomized, controlled study of 223 HF patients using a structured 1-hour, one-on-one teaching protocol led to significantly fewer deaths, rehospitalizations, or days hospitalized during follow-up.[91] In addition to improving self-care adherence, cost of care in the patients receiving the intervention was lower than in control subjects.

Table 8.2. Modifiable Factors Leading to Hospital Readmissions for HF

- Inadequate patient and family or caregiver education and counseling
- Poor communication and coordination of care among health care providers
- Inadequate discharge planning
- Failure to organize adequate follow-up care
- Clinician failure to emphasize nonpharmacologic aspects of HF care, such as dietary, activity, and symptom monitoring recommendations
- Failure to address the multiple and complex medical, behavioral, psychosocial, environmental, and financial issues that complicate care, such as older age, presence of multiple comorbidities, lack of social support or social isolation, failure of existing social support systems, functional or cognitive impairments, poverty, presence of anxiety or depression
- Failure of clinicians to use evidence-based practice and follow published guidelines in the prescription of pharmacologic and nonpharmacologic therapy

Disease Management Programs

Practitioners who care for patients with HF are challenged daily with preventing common, recurrent rehospitalizations for exacerbations. Most of the staggering cost associated with the care of HF patients is attributable to these hospitalizations.[92–94] As many as one-half to two-thirds of hospital readmissions are thought to be preventable with attention to modifiable factors,[95–99] which include those listed in Table 8.2.[1,4,87,96,100–108]

Recognizing the deficiencies in traditional or "usual care"[109] has led to the testing of comprehensive, integrated, interdisciplinary disease management models of care that demonstrate markedly improved outcomes.

Recommendation

8.7 Patients recently hospitalized for HF and other patients at high risk for HF decompensation should be considered for comprehensive HF disease management. High-risk patients include those with renal

insufficiency, low output state, diabetes, chronic obstructive pulmonary disease, persistent New York Heart Association (NYHA) class III or IV symptoms, frequent hospitalization for any cause, multiple active comorbidities, or a history of depression, cognitive impairment, inadequate social support, poor health literacy, or persistent nonadherence to therapeutic regimens. (Strength of Evidence = A)

Background

Disease management is "a comprehensive, integrated system for managing patients…by using best practices, clinical practice improvement…and other resources and tools to reduce overall cost and improve measurable outcomes in the quality of care''.[110] A number of disease management programs have been studied. They fall into 3 broad categories: (1) HF clinics [19,111–126] (2) care delivered in the home or to patients who are at home [18,83,90,105,127–139] and (3) telemonitoring.[140–146] Clinics or services designed solely for the administration of intravenous infusions, or which consist of only a single component of HF care, are not considered HF disease management programs and generally have not provided evidence of effectiveness.

HF clinics are disease management programs in which service is provided primarily in an outpatient clinic setting where patients come to receive care from practitioners with expertise in HF. HF clinics provide optimization of drug therapy, patient and family/caregiver education and counseling, emphasis on self-care, vigilant follow-up, early attention to signs and symptoms of fluid overload, coordination of care with other providers, quality assessment, and increased access to the health care provider.

Although some of the studies evaluating disease management in HF clinics were randomized, controlled trials,[113,114,119,123,126] most compared data before and after program implementation. These studies consistently show that HF patients receiving care in a HF clinic experience a reduction in subsequent hospitalizations and hospital days, higher quality of life, and an improvement in functional status. This model appears to be cost-effective, because the increased costs of specialty care are offset by fewer rehospitalizations and/or improvements in quality of life endpoints.[147–149] Improved survival was seen in one of the randomized, controlled trials.[123] The largest study of clinic-based disease management to date, the Coordinating Study Evaluating Outcomes of Advising and Counseling in Heart Failure (COACH) demonstrated a non-statistically significant 15% reduction in mortality in 1049 patients randomized to a nurse-based HF disease management intervention as compared to usual care. However, no differences between groups were observed in the primary endpoints of all-cause mortality or HF hospitalization, or the number of days lost because of death or hospitalization over 18 months of follow-up.[126] The lack of effect on the primary endpoints in this study may have been due to a lower than anticipated event rate, and closer follow-up than anticipated in the usual care group. In a meta-analysis of 29 randomized trials of multidisciplinary HF disease management programs involving 5039 patients, disease management programs were associated with significantly lower mortality and hospitalization rates. The majority of the trials included in this meta-analysis that analyzed cost-effectiveness (15 of 18) demonstrated that the strategies were cost saving.[150] Another meta-analysis included 54 studies, 27 of which were randomized and 27 of which were not randomized.[151] The findings of this analysis revealed that among the randomized studies, disease management programs were associated with reductions in all-cause hospitalizations, cardiovascular and HF specific hospitalizations, and the combined endpoint of hospitalization or death.[151]

Another model features HF-specific care delivered in the home or to patients at home. Many of these programs use a case management approach. Included in this group are examples of true multidisciplinary and collaborative HF care.[83,90,131,152] Characteristics shared by these programs include patient and family/caregiver education and counseling, emphasis on self-care, vigilant follow-up, early attention to signs and symptoms of fluid overload, coordination of care with other providers, increased access to the health care provider, and attention to social and financial barriers to adherence.

Studies of patients receiving care in the wide variety of home-based programs showed significantly fewer total and HF rehospitalizations, fewer days per hospitalization, improved quality of life, lower health care costs, and improved survival. [83,90,105,127–129,131,133–136,152,153] Several were randomized controlled trials that showed positive results for endpoints such as time to first hospitalization, days in the hospital, unplanned readmissions, and deaths out of the hospital.[127,129,131,134,153] In the meta-analysis by McAlister et al, disease management programs that focused on enhancing patient self-care activities reduced HF hospitalizations by 34%, and all-cause hospitalizations by 27%, but they had no effect on all-cause mortality.[150]

In the third category of disease management programs, computer technology and telephone data transmission are used to monitor patients' weight, blood pressure, heart rate, and in some cases other physiologic parameters. These programs have much less personal contact with a health care provider than the home-based programs, and many lack an educational component. Most of the studies conducted using telemonitoring techniques were small, with one exception.[146] Because of these study limitations, findings concerning this category of disease management programs remain equivocal. In the meta-analysis by McAlister et al, disease management strategies using telephone contact were associated with a reduction in HF hospitalizations, but not mortality or all-cause hospitalization.[150]

Studies of HF disease management using the clinic and home-based care models provide convincing evidence that it is possible to significantly reduce rehospitalization rates

and costs and improve functional status and quality of life for HF patients. Although evidence of a clinical benefit was not demonstrated statistically in the COACH trial, a potentially clinically relevant reduction in all-cause mortality was noted, and it is plausible that a higher than expected level of care was provided in the usual care arm, thus limiting the ability to detect significant between-group differences.[126] A growing number of adequately powered studies and published meta-analyses have demonstrated a positive effect on survival by HF disease management.[123,127,136,150,151] This effect appears to be due to improved patient self-care. Programs focusing on self-care skills demonstrate gains equal to or greater than those seen with programs that improve drug therapy.[18,123]

Recommendations

8.8 It is recommended that HF disease management programs include the components shown in Table 8.3 based on patient characteristics and needs. (Strength of Evidence = B)

Table 8.3. Recommended Components of a HF Disease Management Program

- Comprehensive education and counseling individualized to patient needs
- Promotion of self care, including self-adjustment of diuretic therapy in appropriate patients (or with family member/caregiver assistance)
- Emphasis on behavioral strategies to increase adherence
- Vigilant follow-up after hospital discharge or after periods of instability
- Optimization of medical therapy
- Increased access to providers
- Early attention to signs and symptoms of fluid overload
- Assistance with social and financial concerns

8.9 It is recommended that HF disease management include integration and coordination of care between the primary care physician and HF care specialists and with other agencies, such as home health and cardiac rehabilitation. (Strength of Evidence = C)

8.10 It is recommended that patients in a HF disease management program be followed until they or their family/caregiver demonstrate independence in following the prescribed treatment plan, adequate or improved adherence to treatment guidelines, improved functional capacity, and symptom stability. Higher risk patients with more advanced HF may need to be followed permanently. Patients who experience increasing episodes of exacerbation or who demonstrate instability after discharge from a program should be referred again to the service. (Strength of Evidence = B)

Background

Essential Elements of Disease Management. Every successful HF disease management program has a comprehensive education and counseling component. Programs should include intensive guideline-based education and counseling with emphasis on behavioral strategies to increase adherence and counseling to address patients' individual barriers to engaging in self-care. Education should include diet, medications, weighing, symptoms heralding worsening HF, and the importance of seeking early treatment for these symptoms. Promotion of self-care is a fundamental component of successful programs and the foundation upon which disease management is based. Frequent follow-up in some form and increased access to health care providers also appear to be vital components. Optimization of medical therapy is an important aspect. Because the majority of rehospitalizations for exacerbation are the result of fluid overload[98] some mechanism for addressing early signs of fluid overload is essential. In many programs, educating patients about flexible diuretic regimens is successful. When patients or their family or caregiver are unable or unwilling to assume significant responsibility, home visits by a nurse or "drop-in" visits to a HF clinic are options. Assistance with social and financial concerns and coordination of care among all agencies involved are additional important components of HF disease management.

A recent meta-analysis examined randomized controlled trials of disease management programs from 1995−2005 in order to determine the characteristics that were common to successful programs.[154] They found that successful disease management always had multiple components, including an in-hospital phase of care, intensive patient education, self-care supportive strategy, optimization of the medical regimen, and ongoing surveillance and management of clinical deterioration. It was considered fundamental that a cardiac nurse and cardiologist be actively involved and that the delivery of follow-up care was flexible.

Advance Directives and End-of-Life Care

Overview

HF has a worse prognosis than many common cancers,[155] and premature death from progressive decompensated HF or sudden cardiac death (SCD) is frequent. Recent advances in HF treatment have resulted in substantial reductions in annual mortality from these modes of death. Nevertheless, the mortality rate in HF remains high, making advance directives and end-of-life care important issues for patients with this condition.

Hospice services or other end-of-life care should only be implemented after full and appropriate application of evidence-based pharmacologic and cardiac device therapies (ie, cardiac resynchronization therapy [CRT]), unless documentation of intolerance or contraindication to such treatments is present. For critically ill patients, clinicians should acknowledge to the patient and their family the potentially life-threatening nature of their condition, and supportive care should be implemented as indicated. In most

cases, adequate time (weeks to months) must be given to allow medical therapies to exert a beneficial therapeutic effect. In addition, issues such as access to care, adherence to medications and other self care behaviors, and knowledge about HF must be addressed. End-of-life care most often includes continuing HF therapies, which may effectively ease symptoms and stabilize or improve quality of life. Failure to implement evidence-based therapies or to comply with quality measures for HF is associated with higher patient mortality.[156] In one hospital system, HF patients with do-not-resuscitate (DNR) orders were less likely to receive quality measures including ACE-inhibitor/angiotensin receptor blocker (ARB) use, non-pharmacologic counseling, or assessment of left ventricular (LV) function as compared to patients without DNR orders, after adjustment for other factors.[157] Discontinuation of medications at the end of life may be considered when taking them becomes burdensome (eg, the patient has difficulty swallowing) or if they do not impact symptoms (eg, statins). Drugs should be discontinued one at a time so that worsening symptoms can be correctly attributed to discontinuation of a specific drug.

A discussion about HF course and prognosis should be conducted with all patients to the extent that they are willing to participate in such a conversation. Several tools, including the Enhanced Feedback for Effective Cardiac Treatment (EFFECT) score[158] and the Seattle HF Score,[159] may help clinicians identify the patient's general prognosis. Secondary analyses of registries and trials have identified several common predictors of death, including low sodium, elevated BUN or serum creatinine, advanced age, and low hemoglobin.[160–164] Data generated from these scores should be presented to the patient and family as an estimated range of times, with the caveat that patients may live longer or shorter than expected.

A discussion of prognosis should acknowledge the fact that death in HF may occur suddenly and unexpectedly in patients who are otherwise well compensated, so patients should be educated on the available strategies to reduce the risk of SCD. In the Candesartan in Heart Failure: Assessment of Reduction in Mortality and Morbidity (CHARM) Preserved study that enrolled patients with NYHA Class II-II HF and preserved left ventricular ejection fraction (LVEF), 29% of subjects died of SCD while 20% died of progressive HF. Non-cardiovascular causes accounted for 30% of deaths, and the remaining 21% died of other cardiovascular causes.[165] In CHARM-Added, 40% of patients with NYHA Class II-III HF and reduced LVEF died of SCD, 28% died of progressive HF, and 20% died of non-cardiovascular causes. However, in subjects with a reduced LVEF, mortality was double that observed in those with a preserved LVEF so the absolute mortality from SCD was much higher in patients with reduced LVEF compared to those with preserved LVEF.[166] In the Metoprolol CR/XL Randomised Intervention Trial in-Congestive Heart Failure (MERIT-HF), the mortality in subjects randomized to the metoprolol CR/XL group was 5.3%, 8.1%, and 16.7% per patient-year of follow-up for NYHA class II, III, and IV, respectively. The deaths due to progressive HF increased from 12% to 26% to 56% in NYHA Class II, III, and IV, respectively, while SCDs declined from 64% of deaths in NYHA Class II subjects to 59% in class III and to 33% in Class IV subjects.[167] The absolute number of SCDs was 6, 11, and 19 per 100 subjects in NYHA classes II, III, and IV. In the Comparison of Medical Therapy, Pacing, and Defibrillation in Chronic Heart Failure (COMPANION) Trial, NYHA Class IV CRT subjects experienced about 15 SCDs per hundred.[168] Thus, while the percentage of deaths due to SCD is lower in patients with NYHA Class IV HF, the absolute number of SCDs is quite large. This general concept of a decline in the absolute percentage of SCD but a high absolute number has been confirmed recently.[169]

Patients and families may want more specific information about their likely course. A greater proportion of patients with less severe symptoms tend to die from SCD, whereas death is attributed to progressive HF more often in patients with more symptomatic disease.[167] In young patients, progressive HF death typically is heralded by a period of severe symptoms, frequent hospitalizations, and obvious, unremitting clinical deterioration. Some individuals, especially, older, frail individuals, may have severe fatigue as a sign of progressive HF. Shortness of breath can be well managed for most patients and should not be presented as inevitable.

Discussion of end-of-life care can occur when the patient has progressed to a state of severe, refractory HF. This discussion is easier if the patient and family are aware early in the course of HF care that HF leads to death, often over a period of many years. Early in the course of care, clinicians should discuss dying from HF with patients. This conversation should include a discussion about the effectiveness of medication management, the use of CRT (if indicated) to modify the course of illness, and the potential risks and benefits of implantable defibrillators to reduce the chance of a SCD. Some data suggest that patients prefer to be informed about issues related to their disease and its prognosis when they are relatively well.[170] In addition, patients want to be aware of the prognosis of their condition, but they desire that this information be balanced with hope that they have the potential to respond to available therapeutic measures.[170] To optimize interventions and approaches to care, it is important to understand whether a patient would want an attempt at resuscitation or natural death.[171]

In considering these issues, it is important to understand the distinction between advance directives and end-of-life care. Advance directives are decisions or legal documents made or created by individuals and shared with loved ones and health care providers that identify desired or undesired treatments if an individual becomes incapacitated and incapable of making decisions about care. Examples of legal advance directives are shown in Table 8.4. All patients with HF should be encouraged to have advance directives in place before the end-of-life is imminent and should

Table 8.4. Examples of Legal Advance Directives

Legal Advance Directive	Description
Living Will	This document uses standard language in the patient's state of residence, identifying whether specific or general life-prolonging interventions should be initiated (or continued) in the face of imminent death. Some states require 2 physicians to certify that the patient has a ''terminal illness'' for a living will to be enacted.
Durable Power of Attorney for Health Care (DPOA/HC)	This document designates one or more individuals to make health care decisions on behalf of the person at a future time if the person is unable to speak independently. While the DPOA/HC does not typically identify specific interventions or approaches to care desired by an individual, patients should be encouraged to make their proxy aware of undesired states and/or generally preferred approaches to care. Patients with HF should be encouraged to appoint a DPOA/HC. Clinicians should discuss with patients with HF general preferences for care, including preferences for an attempt at resuscitation versus allowing natural death.

designate proxy decision makers in the event they are not able to speak for themselves. The use of advance directives has not been well-studied in patients with HF. End-of-life care refers to care designed to provide symptom relief, comfort, and support for patients and their families when optimal treatments have failed to halt progression of the illness or relieve symptoms and the likelihood is high that death is imminent within the coming weeks to months.

Recommendations

8.11 It is recommended that patient and family or caregiver discussions about quality of life and prognosis be included in the disease management of HF. (Strength of Evidence = C)

8.12 It is recommended that:

a. Seriously ill patients with HF and their families be educated to understand that patients with HF are at high risk of death, even while aggressive efforts are made to prolong life.

b. Patients with HF be made aware that HF is potentially life-limiting, but that pharmacologic and device therapies and self-management can prolong life. In most cases, chronic HF pharmacologic and device therapies should be optimized as indicated before identifying that patients are near end-of-life.

c. Identification of end-of-life in a patient should be made in collaboration with clinicians experienced in the care of patients with HF when possible.

d. End-of-life management should be coordinated with the patient's primary care physician.

e. As often as possible, discussions regarding end-of-life care should be initiated while the patient is still capable of participating in decision-making. (Strength of Evidence = C)

8.13 End-of-life care should be considered in patients who have advanced, persistent HF with symptoms at rest despite repeated attempts to optimize pharmacologic, cardiac device, and other therapies, as evidenced by 1 or more of the following:

- **HF hospitalization[172,173] (Strength of Evidence = B)**
- **Chronic poor quality of life with minimal or no ability to accomplish activities of daily living (Strength of Evidence = C)**
- **Need for continuous intravenous inotropic therapy support[174,175] (Strength of Evidence = B)**

Background

Identification of Patients Who Are Near the End of Life. Some patients with HF exhibit episodes of frequent decompensation requiring hospitalization. Although a roller-coaster pattern of decompensation may occur in advanced HF despite aggressive therapy, in some patients, events will be related to reversible causes, such as dietary sodium or fluid indiscretion, medication nonadherence, contraindicated medications, inadequate medical therapy, new onset atrial fibrillation, or acceleration of ventricular rate in patients in chronic atrial fibrillation.

After identifiable causes of decompensation are eliminated and proven therapies have been aggressively applied, end-of-life care should be considered if patients still experience a marked decline in functional ability and quality of life. Typically, these patients have severe LV systolic dysfunction or severe restrictive diastolic dysfunction and evidence of marked cardiac decompensation. They often have significant renal insufficiency and hypotension that may limit the application of effective therapy. This clinical picture persists despite intensive attempts at pharmacologic management both in inpatient and outpatient settings. Elderly patients with HF may also approach the end of life in the context of progressive frailty or with other significant medical problems. HF in this population is often accompanied by cognitive problems and increasing need for assistance with care.

Recognition of End-stage HF. Patients with HF and their caregivers often do not appreciate the life-limiting nature of their illness.[176] HF is a chronic disorder and often progresses to death.[177] Despite the concern that a discussion of prognosis might be discouraging and have a negative impact on psychological and physical morbidity,[178] discussions about dying should occur in the course of care for patients with HF. These conversations should be coupled with discussions on ways patients can manage HF (i.e.,

through self-care maintenance and management behaviors (see sections 8.1−8.6).[179] Early in the course of illness and in the context of a discussion of the importance of self management, the clinician should acknowledge that HF is rarely curable and will ultimately lead to death. This information should be partnered with encouragement that good quality of life can often be achieved with evidence-based pharmacologic and device therapies. Patients should be educated on the possibility of SCD and available strategies to reduce the risk of this event, and clinicians should assess the patients' wishes regarding the implementation of these strategies (i.e. placement of implantable cardioverter defibrillator (ICD), cardiopulmonary resuscitation [CPR]). When patients develop refractory HF despite aggressive medical therapy, clinicians should discuss their worsened prognosis and options for care. It is reasonable to have discussions about the possibility of death with the patient and their family during any period of severe instability (i.e. during hospitalizations for HF, and/or in the setting of hemodynamic compromise or hypoxemia). Recent evidence has shown that the majority of family members or surrogate decision makers of critically ill patients wanted physicians to accurately inform them of the patient's prognosis.[180]

Decision-Making at End of Life. Experience from HF centers caring for patients dying from progressive HF suggests that decisions about termination of life-prolonging therapy are usually made by the patient and family after discussions with their health care provider about prognosis and goals, although such open discussions can be challenging for patients and clinicians.[171,181,182] Decisions related to end-of-life care may be made during periods of relative compensation; however, clinicians should be prepared to guide patients and families in decision making in situations of decompensation as well. Because patients with HF approaching end of life may have periods of confusion, delirium, somnolence, or inattention and need someone else to make decisions, a designated surrogate decision maker or durable power of attorney for health care is especially important at this time.

Recommendations

8.14 It is recommended that end-of-life care strategies be individualized and include core HF pharmacologic therapies, effective symptom management and comfort measures, while avoiding unnecessary testing. New life-prolonging interventions should be discussed with patients and care-givers with careful discussion of whether they are likely to improve symptoms. (Strength of Evidence = C)

8.15 It is recommended that a specific discussion about resuscitation be held in the context of planning for overall care and for emergencies with all patients with HF. The possibility of SCD for patients with HF should be acknowledged. Specific plans to reduce SCD (for example with an ICD) or to allow natural death should be based on the individual patient's risks and preferences for an attempt at resuscitation with specific discussion of risks and benefits of inactivating the ICD. Preferences for attempts at resuscitation and plans for approach to care should be readdressed at turning points in the patient's course or if potentially life-prolonging interventions are considered. (Strength of Evidence = C)

8.16 It is recommended that, as part of end-of-life care, patients and their families/caregivers have a plan to manage a sudden decompensation, death, or progressive decline. Inactivation of an implantable defibrillation device should be discussed in the context of allowing natural death at end of life. A process for deactivating defibrillators should be clarified in all settings in which patients with HF receive care. (Strength of Evidence = C)

8.17 Patients with HF receiving end-of-life care should be considered for enrollment in hospice that can be delivered in the home, a nursing home, or a special hospice unit. (Strength of Evidence = C)

Background

Reassessment of Decision-Making. The Study to Understand Prognoses and Preferences for Outcomes and Risks of Treatment (SUPPORT) evaluated 936 patients with severe HF and showed a 19% change in resuscitation decisions over a 2-month period among patients who survived their enrollment hospitalization.[183] In 50% of the cases, the physician's perception of the patient's preference was inaccurate. An analysis of the SUPPORT and Hospitalized Elderly Longitudinal Project (HELP) showed that a HF diagnosis was an independent predictor of attempted resuscitation, whereas other severe diseases (chronic obstructive pulmonary disease, cirrhosis, coma, colon or lung cancer, or multi-system organ failure) were independent predictors of not receiving resuscitation.[184]

End-of-Life Care. The goals of end-of-life care are to meet patients' and their families' goals for length and quality of life to the extent possible, manage debilitating symptoms, and provide support for emotional, social, and spiritual distress. Bereavement support should be provided during the patient's illness and for the family after the patient's death. In most cases, evidence-based HF care or even aggressive treatment should be continued to meet these goals. In some cases, time-limited trials of aggressive treatment can be used to help providers and patients understand whether or not a patient may be responsive to such treatment. Hospitalization for management of congestion or a trial of intravenous treatment at home or under hospice

care to reduce symptoms are examples of appropriate end-of-life medical care for HF.

Symptom Management. Patient-centered care dictates that symptoms be managed to the level desired by patients and families when possible. Inadequate symptom relief is distressing to patients and their families and negatively affects quality of life, as well as the ability of patients to complete life closure tasks.[185]

Since some therapies to manage HF symptoms may influence duration of survival, it is important for physicians to fully assess a patient's desires regarding the balance of symptom management and prolongation of life. In a time-trade-off study of 287 patients with advanced HF in the ESCAPE (Evaluation Study of Congestive Heart Failure and Pulmonary Artery Catheter Effectiveness) study, 49% indicated they would not be willing to trade survival time to feel better. In the subgroup of patients who survived for $<$105 days, 31% reported they would trade almost all of their remaining days to feel well for the time they had left. In contrast, only 6% of patients who survived for 180 days were willing to trade most of their survival days to feel well ($P=0.0015$).[186]

In an analysis of 91 HF patients (48 with NYHA class II symptoms and 43 with NYHA class IV symptoms), treatment preferences were assessed in relationship to the time trade off score. In this analysis, two specific patient groups were identified. Treatments that improved quality of life at the expense of survival were preferred by 55% of the patients, whereas 45% preferred medical management that prolonged survival time.[187] The description of end-of-life symptoms that may occur with medical management (severe shortness of breath or gasping for air) may have influenced the outcome of this study. Interestingly, these preferences correlated poorly with quality of life, symptom, and overall health scores.[187] This evidence suggests that for some patients, treatment preferences can be decided early in the course of the illness.

As compared to patients with other manifestations of coronary heart disease, patients with HF have a worse health status at the end of life and tend to have more hospitalizations, and more commonly rate their health as fair or poor, have activity restrictions, and report symptoms.[188] An array of symptoms are seen among patients with end stage HF,[189-191] including pain (78%), dyspnea (61%), low mood (59%), sleeplessness (45%), loss of appetite (43%), confusion (40%), constipation (37%), nausea and vomiting (32%), anxiety (30%), and urinary incontinence (29%).[192] Families rated pain, dyspnea, low mood, anxiety, urinary incontinence, and confusion as being the most distressing to patients in the last year of their lives. In the SUPPORT study of patients admitted for acute HF who were considered to have end-stage HF, the three most common symptoms reported by family members in the last 6 months of life were dyspnea, pain, and confusion.[189] The percentage of patients experiencing escalating rates of perceived severe dyspnea and pain increased significantly as death approached. In the last 3 days of life, 63% of all patients with HF experienced severe dyspnea. Current experience may differ as a result of advancements in medical therapies since the early 1990s when SUPPORT was conducted, but nonetheless, adequate symptom management is a high priority for patients and their families. In one study, during the last week of life, 70% of patients' families rated their quality of life as poor to fair. Increases in emotional symptoms, such as anxiety and depression, were reported by families during the 3 days before death. Other studies have confirmed these findings.[193] Analysis of medical records of 80 patients diagnosed with HF revealed that the most common symptoms experienced in the last 6 months of life were breathlessness (88%), followed by pain (75%) and fatigue (69%). Investigators concluded that end-stage patients with HF experience similar symptoms to end-stage cancer patients. In two studies of HF programs, the course to death for patients with advanced HF was frequently progressive metabolic disarray and decreased consciousness.[194,195]

One of the most important components of end-of-life care is good listening and open communication, with particular attention to patients' concerns about management of symptoms, attitudes about dying,[177] ease to access of services, and emotional and spiritual concerns. Symptoms should be treated to the level of comfort desired by the patient and family, recognizing that in some situations a compromise is required between alertness and decreased symptoms.

As previously discussed, pain is present in two-thirds or more of patients with HF, and it is common for patients to have multiple sites of pain. Non-steroidal anti-inflammatory drugs should be avoided in patients with HF, so interventions for arthritis pain should include local steroid injections, low-dose opioids, and physical therapy. Pain related to ischemia is most effectively treated with nitrates and opioids. Dyspnea can be managed with diuretics and opioids. Morphine is inexpensive and effective for dyspnea, but active metabolites can accumulate in patients with end-stage disease because of poor renal function. This accumulation may lead to myoclonus, agitation and delirium. In addition, recent evidence from the Acute Decompensated Heart Failure National Registry (ADHERE) suggests that morphine use may be associated with higher risk of mortality, even after adjustment for other important risk factors.[196] Clinicians should be vigilant for confusion or delirium and attempt to avoid medications or other insults that precipitate or worsen delirium. Antidepressants, sleep aids, sedatives, and complementary therapies can worsen confusion, particularly if pharmacokinetic or pharmacodynamic changes related to HF (i.e. poor hepatic or renal perfusion) or age are not considered. Dose adjustments or extended dosing intervals may be needed to optimize the benefits from these drugs while minimizing cognitive side effects. Gastrointestinal problems, such as loss of appetite, constipation, nausea/vomiting, and fecal incontinence can be managed with diet modifications, appetite enhancers, laxatives, or other medications. Urinary

incontinence is often related to diuretic use and weakness of the urinary sphincter. It may be addressed with a change in the timing of diuretic doses, a urinary catheter, pads or incontinence underwear. Management of fatigue and activity intolerance may require lifestyle modifications including periods of rest with feet elevated or rescheduling of activities to take advantage of changing energy levels. Energy conservation techniques, such as breathing retraining, spacing activities, meditating, or using assistive devices, may be helpful. A low-level exercise program may have both physical and psychological benefits. Home health aides and homemakers can be very helpful in assisting patients to manage activities of daily living and thus conserve energy.

Use of Continuous Intravenous Inotropic or Vasoactive Support and End-of-Life Care. Patients undergoing end-of-life care may respond to continuous intravenous inotropic agents with temporary symptomatic improvement. Utilization of inotropic agents must be undertaken with the understanding that these drugs likely will reduce survival due to an increase in SCD. Health care providers skilled in HF management may use intravenous inotropic infusions for end-of-life care when oral HF pharmacologic therapies fail to stabilize symptoms. The use of inotropic therapy in this population is highly variable.[197] Patients should be informed about the potential risks of inotropic therapy including proarrhythmia and other adverse clinical outcomes such as sepsis due to chronic indwelling venous catheters that might reduce life expectancy despite a possible period of symptomatic improvement.

Periodic reevaluation of continuous intravenous inotropic support is mandatory, because the patient's response to treatment may diminish over time, or the patient may decide that the quality of life gained is offset by the intensity of therapy required. Continuous intravenous inotropic therapies must not be considered as acceptable alternatives to core evidence-based HF pharmacologic and cardiac device based treatments. They should be applied only after careful attempts to manage patients with evidence-based drug and cardiac device therapies. Hospices vary in their provision of intravenous and other therapies, based on agency size and staff education.

Referral to Hospice. Data from 2000 indicate that 8% of all hospice patients have a diagnosis of HF.[198] A survey of hospice centers published in 2005 reported similar findings, with an average of 9% of patients under hospice care having a primary diagnosis of HF.[199] Patients with cancer are routinely referred for hospice care and comprise the majority of hospice patients nationally. Only 1.6% of the 182,898 hospitalization episodes from 2001−2005 in ADHERE resulted in hospice referral; however, ADHERE enrollment was not limited to an end-stage population.[200] Hospices vary in their expertise and practice caring for patients with HF.[201] Clinicians providing care to patients with HF should partner with local hospice agencies to create a plan of care to meet patients' needs. For select patients, referral for hospice services may be an appropriate method of providing palliation when symptoms are refractory, quality of life is poor, and there is functional decline.[202] The Medicare hospice benefit was developed so that individuals could choose such supportive care and still receive Medicare funding.

To be eligible for the hospice benefit, the patient's physician and hospice medical director must certify that the patient has a likely life expectancy of 6 months or less, and the patient must consent to receive hospice in lieu of Medicare A-reimbursed care for his or her terminal illness. This agreement does not preclude other treatments for illnesses or injuries not related to HF, nor does it necessitate abandonment of appropriate HF medical therapy. Patients may withdraw from the hospice program and reenroll at a later date with no penalty. Hospice care is not limited to 6 months; however, the patient's prognosis must be identified as approximately 6 months at specified certification periods (the first two periods are 90 days, followed by an unlimited number of 60 day certifications).

The Medicare hospice benefit includes coverage for all medications and treatments associated with the hospice diagnosis, symptom management, homemaker and home health aide assistance, and chaplain and bereavement support for patients and families. Nursing care, medical supplies and appliances, therapy services and a wide variety of other professional support services necessary to improve quality of life are covered. Physician oversight of care may be provided by the hospice medical director or by a physician of the patient's choice.

There are four levels of hospice care. In the United States, 70% of hospice care is delivered in patients' homes or place of residence (including nursing homes).[203] Respite care up to 5 days per certification period is generally provided in nursing homes under contract. ''General inpatient care'' is provided to manage symptoms or provide services that cannot be provided in other settings—in either a hospital or nursing home. ''Continuous care'' provides 8−24 hours of licensed nursing care in the home for brief periods of time to manage complex problems or provide caregiver education. Hospice care is reimbursed by Medicare and most insurances at a specified daily rate, regardless of the medications, treatments or services provided.

Advance Directives and Risk of Sudden Death. SCD in a patient with compensated HF is a relatively common cause of death. Most SCDs occur outside the hospital, often at home or in the presence of a family member. Families commonly express the need to know how to respond in a cardiac emergency and report that this learning need is often unmet by health care professionals.[204] Patients report wanting their families to know what to do in an emergency.[204,205] A discussion with patients and families about the patient's wishes regarding resuscitation can include information about the effectiveness of resuscitation and its

sequelae.[206] Patients' wishes need to be clear to all healthcare providers and family care givers, and they should be documented in a written advance directive when possible. Discussions regarding patient and family preferences should be undertaken before an acute crisis develops.

Information on Cardiopulmonary Resuscitation. When patients and families make the choice to attempt resuscitation, family members can be advised how to obtain CPR training. Many clinicians express concern over the ability of families of high-risk cardiac patients to learn CPR, and the potential guilt they might feel if resuscitation fails. In fact, the majority of family members of patients at risk for SCD can successfully learn CPR, are not burdened by responsibility or guilt, and use CPR appropriately when the occasion arises.[207,208]

Choice to Allow Natural Death. When patients and families decide against resuscitation attempts, they need to be told what to do when death occurs outside the hospital. Without prior information, most people call 911 or a similar emergency medical system number. In some states, this action may end in unwanted resuscitation and prolonged life support efforts. Many states have statutes directing emergency response personnel to comply with written physician orders for resuscitation (such as the Physician Order for Life Sustaining Treatment originally developed in Oregon).[209] A better option is to have a family member call a health care provider who knows the patient, has been informed of the patient's preference to not attempt resuscitation, and is willing to certify the cause of death.

As more patients with HF have ICDs implanted, it is important to plan what actions to take when patients are near the end of life. Defibrillation devices can be inactivated for those end-stage patients who do not desire resuscitation. A clear process for defibrillator deactivation should be identified to facilitate this step in advance of imminent death. A recent survey revealed that roughly 60% of cardiologists, 88% of geriatricians, and 95% of family physicians or internists had 2 or fewer conversations with patients and families about deactivation of implanted defibrillators.[210] Kelley et al reported the results of a similar survey designed to assess physician management practices regarding ICD use near the end of life.[181] Only 13% of the physician respondents accepted primary responsibility for discussions regarding device inactivation, 10% responded that another doctor should discuss, and 7% felt the patient or family should bring it up first.[181] These data suggest that communication among patients and physicians regarding ICD therapy at the end of life is needed.

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Section 9: Electrophysiology Testing and the Use of Devices in Heart Failure

General Considerations

Recommendation

9.1 It is recommended that the decision to undertake electrophysiologic (EP) intervention, including implantable cardioverter defibrillator (ICD) implantation, be made in light of functional status and prognosis based on severity of underlying HF and comorbid conditions. If an ICD is considered due to left ventricular (LV) dysfunction which is of recent onset, LV function should be reassessed, ideally after 3−6 months of optimal medical therapy. (Strength of Evidence = C)

Background

Trials supporting the use of EP devices in HF for prevention of sudden cardiac death (SCD) typically have excluded patients with persistent New York Heart Association (NYHA) IV HF, patients in cardiogenic shock, those with irreversible brain damage, and those with comorbidities and an expected survival of <1 year. Recent trials have excluded patients with a recent myocardial infarction (MI), a coronary revascularization procedure within 3 months or ongoing ischemia.[1] This allows adequate time from the index ischemic event for the appropriate application of pharmacologic therapy and for the beneficial effects of the primary therapeutic strategy to be manifest before consideration of device therapy. Patients are not good candidates for device implantation if they have significant psychiatric illness that may be aggravated by device implantation or are not expected to be compliant with systematic follow-up.

EP Testing and Evaluation of Syncope

Recommendation

9.2 Immediate evaluation is recommended in patients with HF who present with syncope. In the absence of a clear identifiable noncardiac cause, consultation with an EP specialist should be obtained. (Strength of Evidence = C)

Background

Typically, ICD implantation is accepted as first-line therapy in patients presenting with syncope of unknown origin who have hemodynamically significant sustained ventricular tachycardia (VT) induced at EP study (EPS). This indication is supported by substantial observational data showing an annual cardiovascular mortality of approximately 20% in such patients, much of which appears to result from sudden death.[2−5] A related indication includes patients with recurrent syncope of uncertain etiology in the presence of ventricular dysfunction when other causes of syncope are excluded. Such cases, usually associated with nonischemic dilated cardiomyopathy, may suffer a risk of SCD as high as 45%.

Few studies have been conducted in the setting of nonischemic dilated cardiomyopathy and syncope. One evaluated patients with syncope, inducible ventricular arrhythmias, and previously documented VT.[6] ICDs proved useful in reducing arrhythmic deaths. Another study compared dilated nonischemic cardiomyopathy patients with unexplained syncope and an ICD with a group of cardiac arrest survivors with ICDs.[7] It demonstrated that the number of appropriate ICD discharges in the syncope group were similar to those of the cardiac arrest group. Such data, although rudimentary, do provide insight into recommending strategies for clinical ICD implantation until more definitive evidence is available.

Recommendation

9.3 Routine EP testing is not recommended in patients with LV systolic dysfunction who have asymptomatic nonsustained ventricular tachycardia (VT) in the absence of prior infarction. (Strength of Evidence = B)

Background

The predictive accuracy of EP testing in nonischemic cardiomyopathy is limited.[8−12] On the one hand, when such patients present with spontaneous ventricular arrhythmias, ventricular arrhythmias can be induced in more than two-thirds.[9] On the other hand, EP testing is less likely to induce VT in patients with nonischemic dilated cardiomyopathy and a presentation of aborted SCD or nonsustained VT than in patients with underlying coronary artery disease.[8,11,12] Furthermore, EP can induce ventricular arrhythmias in 10% to 40% of these patients, even in the absence of previous clinical arrhythmias.[8] Thus EP testing is not useful for risk stratification in nonischemic cardiomyopathy. Overall, the magnitude of LV dysfunction remains the best predictor of both SCD and total mortality in this population.[12]

In the setting of ischemic cardiomyopathy and prior infarction, routine EP risk stratification is not recommended. EP testing followed by ICD implantation for inducible sustained VT can be considered for patients in whom there is concern that they are at risk for SCD, but who do not meet guidelines based on the severity of chronic LV dysfunction. This approach may be considered in patients with nonsustained VT who are more than 5 days after MI, or who have had recent revascularization, or who have LV ejection fraction (LVEF) >0.35.[13,14]

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Prophylactic ICD Placement

Recommendations

9.4a Prophylactic ICD placement should be considered in patients with a LVEF ≤35% and mild to moderate HF symptoms:
- **Ischemic etiology (Strength of Evidence = A)**
- **Non-ischemic etiology (Strength of Evidence = B)**

See Recommendation 9.1 for additional criteria.

9.4b In patients who are undergoing implantation of a biventricular pacing device according to the criteria in recommendations 9.7-9.8, use of a device that provides defibrillation should be considered. (Strength of Evidence = B)

See Recommendation 9.1 for additional criteria.

9.5 ICD placement is not recommended in chronic, severe refractory HF when there is no reasonable expectation for improvement or in patients with a life expectancy of less than 1 year. (Strength of Evidence = C)

Background

More than 80 percent of patients who experience a life-threatening ventricular tachyarrhythmia do not survive to benefit from an ICD. Thus, the concept of the ICD for primary prevention of SCD has received considerable attention. Several large trials have been conducted to address primary prevention.[14–19] The Sudden Cardiac in Heart Failure Trial (SCD-HeFT)[15] tested the hypothesis that amiodarone or an ICD would improve survival compared with placebo in patients with HF. The study enrolled 2521 patients with NYHA II or III HF and an LVEF <35% of either ischemic or nonischemic etiology. Patients were randomly allocated to treatment with an ICD, amiodarone, or placebo. Background therapy was strong: 87% were on angiotensin-converting enzyme (ACE) inhibitors or angiotensin receptor blockers (ARBs) and 78% on beta blockers at last follow-up. ICD therapy decreased mortality by 23% compared with control, with an absolute reduction in mortality of 7% over a mean follow-up of 45 months. The ICD benefit was consistent across ischemic and nonischemic etiologies of HF. Subgroup analysis found benefit in NYHA Class II, but failed to demonstrate benefit from ICDs in patients with NYHA Class III, although such subgroup findings must be interpreted cautiously. A similar subgroup differentiation between NYHA class II and III has not been observed in any other ICD trial.[1,20] There was no benefit for amiodarone.

Trials in patients with ischemic cardiomyopathy, including patients with and without HF symptoms, but excluding Class IV HF, also support benefit of an ICD in reducing total mortality. The Multicenter Automatic Defibrillator Implantation Trial (MADIT)-I enrolled patients with a mean LVEF of 26%, a prior MI, unsustained VT, and inducible VT at EPS. Those randomized to receive an ICD had a 54% reduction in total mortality at 27 months over those who had been given ''conventional'' antiarrhythmic therapy.[14] The Multicenter Unsustained Tachycardia Trial (MUSTT) randomized patients with an LVEF ≤40% and an inducible sustained VT into a group receiving beta blockers and ACE inhibitors or a group receiving these agents plus antiarrhythmics or, if they did not respond, an ICD. Over a 5-year follow-up, those receiving the ICD experienced a 27% lower risk of arrhythmic death or cardiac arrest. Total mortality was reduced by 20%.[18] MADIT-II showed a significant survival benefit in patients with prior MI and LVEF ≤30%, but also a trend toward increased HF episodes in patients receiving an ICD.[1] In contrast, a study of patients undergoing coronary artery bypass (CABG) surgery who have LV dysfunction and abnormal signal-averaged electrocardiograms, but no symptomatic ventricular arrhythmias, found no benefit for prophylactic ICD implantation.[16]

A trial of ICDs for patients with nonischemic dilated cardiomyopathy and nonsustained VT reported a favorable trend for mortality reduction that did not reach statistical significance. A meta-analysis of trials in patients with nonischemic cardiomyopathy and the SCD-Heft trial support a survival benefit for ICDs in patients with nonischemic cardiomyopathy.[15,21]

In evaluating these trial results, it must be remembered that numerous factors can impact ICD effectiveness, including the population tested, mode of implantation, concurrent risk of death (eg, concomitant CABG surgery and its inherent risk), background medical therapy, and the influence of ICDs on nonarrhythmic deaths. For example, only 5% of the control group in MADIT was on beta-antagonist therapy, compared with 27% in the treatment arm. It is likely that this contributed to the decrease in cardiac nonarrhythmic deaths in the ICD group.[14] These trials all exclude patients with severe NYHA functional class IV HF, although the Comparison of Medical Therapy, Pacing, and Defibrillation in Heart Failure (COMPANION) trial, examining biventricular pacing with or without concomitant ICD, included some NYHA class IV patients.[17] In such patients, ICD implantation is under consideration as a ''bridge'' to transplant.[22]

Unresolved Issues

Timing of ICD Placement. Time on background therapy is a significant issue. All trials of ICDs have enrolled patients receiving stable doses of appropriate medical therapy, including beta-blockers and ACE inhibitors or ARBs. Furthermore, it is well known that treatment with these agents, particularly beta blockers, for a period of several months frequently results in reduction in LV volumes and improvement or normalization of LVEF. For these reasons, it is appropriate to delay consideration of ICD implant, particularly in the setting of newly diagnosed nonischemic dilated

cardiomyopathy, until after several months of appropriate medical therapy. Although there is no agreement regarding the ideal treatment duration prior to reevaluation of LVEF for consideration of ICD placement, data regarding the time course of reverse remodeling following institution of beta-blocker therapy support a period of 3 to 6 months. Although physicians may choose to place a prophylactic ICD in selected patients prior to such a course of therapy, studies to support such a practice are not available.

Background Therapy. Device effectiveness generally is studied in patients already on background medical therapy. Studies establishing the additional benefit of new agents change the definition of standard or optimal background medical therapy. For example, a recent study of an aldosterone antagonist showed a 15% reduction in total mortality and a 17% reduction in cardiovascular mortality on top of standard medical therapy, mainly because of a 21% reduction in SCD.[23]

Significance of Arrhythmias Detected by ICDs. Trials of prophylactic ICDs have shown that the occurrence of an episode of VT or ventricular fibrillation (VF) is a marker for increased mortality and HF hospitalizations despite effective termination of VT/VF by the ICD.[24–27] VT may be a marker for deterioration of ventricular function. When a patient experiences sustained VT detected by the ICD a careful evaluation and reassessment of HF status and therapy is warranted. The impact of therapies to reduce VT episodes is not clear, although ICD shocks reduce quality of life, and prevention is warranted.

Family History of Sudden Death. There are no systematic data to guide therapy when there is a family history of SCD. This includes patients with familial cardiomyopathy with a history of SCD in 1 or more sibling or parent. In such patients routine implantation of an ICD cannot be routinely recommended, but implantation may be considered on an individual basis after careful consideration of the circumstances.

Recommendation

9.6 ICD implantation is recommended for survivors of cardiac arrest from ventricular fibrillation or hemodynamically unstable sustained VT that is not due to a transient, potentially reversible cause, such as acute MI. (Strength of Evidence = A)

Background

Several studies have shown that ICDs reduce mortality in SCD survivors to a greater extent than antiarrhythmic drug therapy.[28–30] The largest of these trials enrolled 1016 patients who survived cardiac arrest, sustained VT with syncope, or sustained VT in the presence of an LVEF <40% and symptoms suggesting severe hemodynamic compromise. Patients were randomized to receive therapy with either an ICD or an antiarrhythmic drug, generally amiodarone. Survival throughout the trial was superior for patients randomized to ICD therapy. A second study randomized survivors of cardiac arrest equally among 4 treatment arms: ICD, amiodarone, metoprolol, or propafenone. The propafenone arm was terminated prematurely because of excessive mortality. The 2-year mortality was similar for patients randomized to metoprolol and amiodarone (19.6%) but significantly lower in patients randomized to ICD therapy (12.1%).

Many patients in these trials had reduced LVEF and HF. The mean LVEF in one was 39%; in another it was 32%. The survival benefit of ICD was greatest in patients with an LVEF <35%.

A meta-analysis grouping the results of these three trials indicates that therapy with ICDs resulted in a 27% reduction in total mortality.[31] This mortality reduction is due exclusively to a reduction in arrhythmic deaths, particularly in the presence of LV dysfunction.[32]

Biventricular Resynchronization Pacing

Recommendations

9.7 Biventricular pacing therapy is recommended for patients in sinus rhythm with a widened QRS interval (≥120 ms) and severe LV systolic dysfunction LVEF (≤35%) who have persistent, moderate to severe HF (NYHA III) despite optimal medical therapy. (Strength of Evidence = A)

9.8 Biventricular pacing therapy may be considered for patients with atrial fibrillation with a widened QRS interval (≥120 ms) and severe LV systolic dysfunction LVEF (≤35%) who have persistent, moderate to severe HF (NYHA III) despite optimal medical therapy. (Strength of Evidence = B)

9.9 Selected ambulatory NYHA IV patients in sinus rhythm with QRS ≥120 ms and LV systolic dysfunction may be considered for biventricular pacing therapy. (Strength of Evidence = B)

9.10 Biventricular pacing therapy may be considered in patients with reduced LVEF and QRS ≥ 150 ms who have NYHA I or II HF symptoms. (Strength of Evidence = B)

9.11 In patients with reduced LVEF who require chronic pacing and in whom frequent ventricular pacing is expected, biventricular pacing may be considered. (Strength of Evidence = C)

Background

Large observational studies performed in patients with advanced HF have demonstrated that right ventricular (RV) pacing results in worsening symptoms and long-term outcome.[33] This is most likely because of the

development of RV pacing-induced left bundle branch block, resulting in intra- and interventricular dyssynchrony with resultant worsening of left and RV systolic and diastolic function. An analogous phenomenon is seen in patients with advanced HF and bundle branch block. Indeed, the majority of patients with HF have interventricular conduction delay, and up to 30% to 50% have manifest bundle branch block caused by direct pathologic involvement of specialized conduction or by scarring of the myocardium.[34] In those with conduction delay, pacing from the LV or simultaneously from the basal-lateral LV and RV can reduce the delay between septal and posterolateral contraction, to ''resynchronize ventricular contraction.'' Cardiac resynchronization therapy (CRT) seeks to normalize depolarization to improve the efficiency of ventricular contraction and ventricular septal motion, decrease atrioventricular (AV) valve regurgitation, and increase diastolic filling time.[35]

Isolated Biventricular Pacing. The early promise of biventricular pacing[34,35] was tested in the Multicenter InSync Clinical Study (MIRACLE),[36] which randomized 453 patients to activation or nonactivation of cardiac resynchronization, using a double-blind study design. Inclusion criteria were NYHA III/IV, QRS >130 ms, LVEF $<35\%$, and LV end-diastolic dimension >55 mm, as determined by echocardiography. Patients were required to be on optimal medical therapy, defined as ACE inhibitors and beta blockers, for 1 to 3 months before inclusion. Resynchronization improved symptoms, quality of life, and exercise capacity, while reducing LV dimension and improving LVEF at 6 months. Hospitalization or intravenous medications for HF treatment were both reduced by approximately 50%. There was no difference in cardiac or all-cause mortality. This study was not subjected to an intention-to-treat analysis, because randomization occurred only after successful device implantation. The Cardiac Resynchronization-Heart Failure (CARE-HF) study enrolled 813 patients with NYHA class III-IV HF resulting from LV systolic dysfunction and cardiac dyssynchrony with an LVEF $\leq 35\%$ and a QRS duration ≥ 120 ms despite standard medical therapy.[37] After a follow up of just under 30 months, the CRT-treated patients showed a significant benefit in terms of the primary end point of all-cause mortality and unplanned hospitalization (HR 0.63, $P < .001$) and the secondary end point of all-cause mortality (HR 0.64, $P < .002$). Those in the CRT group also showed improved LVEF, NYHA class, end-systolic volume, mitral valve function, blood pressure, and quality-of-life indices. It should be noted that for those patients with a QRS lengthening of 120−149 ms, echocardiographic confirmation of mechanical dyssynchrony was required. This subselection criterion could have favorably influenced the outcomes by preferential enrollment of those more likely to respond to CRT. It is not known how many patients were excluded by this criterion.

Virtually all randomized trials of CRT have required subjects to be in sinus rhythm at the time of randomization. Thus few data are available to determine the benefits of CRT in patents with atrial fibrillation. Retrospective studies and a meta-analysis suggest that patients with chronic atrial fibrillation may benefit from CRT though the benefits may be less than in patients with sinus rhythm.[38] Patients with previous AV nodal ablation and RV pacing may be most likely to benefit from CRT.[39] Prior to considering CRT in a patient with atrial fibrillation, it is important to determine if rate control is adequate to allow biventricular pacing.[40]

Biventricular Pacing With ICD. Initial studies of biventricular pacing with an ICD[41] led to the COMPANION trial,[17] which enrolled patients with HF and NYHA Class III or IV symptoms despite maximized medical therapy. Inclusion criteria included a QRS duration ≥ 120 ms and a PR interval >150 ms. The trial had 3 treatment arms: optimal pharmacologic therapy (OPT), optimal pharmacologic therapy plus biventricular pacing (CRT), and biventricular pacing plus backup ICD therapy (CRTD). In contrast to all others, this study was powered to evaluate a primary endpoint of combined all cause mortality and hospitalization. Data were analyzed using an ''intention to treat'' statistical approach. Of the 1580 patients randomized, 1080 were implanted with a CRT pacer or defibrillator (CRTD). As compared with patients treated with medical therapy only, there was a statistically significant event rate reduction in the primary combined endpoint of total hospitalization and total mortality at 1 year in the CRT and CRTD groups, as well as in the combined endpoint of death and hospitalization for HF. There was a trend toward reduced mortality in the CRT-alone group, although this finding did not reach statistical significance.

Asymptomatic or Mild HF symptoms. MADIT-CRT enrolled and followed 1820 patients with ischemic or nonischemic cardiomyopathy, a LVEF of 30% or less, a QRS duration of 130 msec or more, and NYHA class I or II symptoms.[42] Patients were randomly assigned to receive CRT plus an ICD or an ICD alone. The primary end point was death from any cause or a nonfatal heart-failure event (whichever came first). The primary end point occurred in 17.2% of the CRT-ICD group and 25.3% of the ICD only group (hazard ratio in the CRT-ICD group, 0.66; 95% confidence interval [CI], 0.52 to 0.84; $P=0.001$). The superiority of CRT was present in patients with both ischemic and non-ischemic cardiomyopathy and resulted from a 41% reduction in the risk of heart-failure events, a finding that was evident primarily in a prespecified subgroup of patients with a QRS duration of 150 msec or more. CRT was associated with a significant reduction in LV volumes and improvement in the LVEF. There was no significant difference between the two groups in the overall risk of death, with a 3% annual mortality rate in each treatment group.[42]

Biventricular Pacing when Conventional Pacing is Indicated. There are few data concerning the use of CRT in either patients with reduced LVEF HF and a QRS ≥ 120 msec who have an additional indication for

ventricular pacing or for those who would likely have a significant burden of RV pacing following ICD implantation. However, substantial data exist to suggest that CRT rather than conventional RV pacing may be considered in these patients. The Homburg Biventricular Pacing Evaluation (HOBIPACE) prospectively randomized 30 subjects with standard indications for pacing and reduced LV function as determined by an LVEF ≤40% or an LV end diastolic diameter ≥60 mm to RV or biventricular pacing.[43] Peak oxygen consumption, BNP levels, and LVEF were improved in the CRT group compared to the RV pacing group. In another study, patients with chronic atrial fibrillation who had AV junction ablation were randomized to either RV or biventricular pacing. At 6 months post-ablation, patients treated with cardiac resynchronization had a significant improvement in 6-minute walk distance, (31%) above baseline (82.9 +/− 94.7 m), compared to patients receiving RV pacing, (24%) above baseline (61.2 ± 90.0 m) (P = 0.04). There were no significant differences in the quality-of-life parameters. At 6 months post-ablation, the LVEF in the biventricular group (0.46 ±− 0.13) was significantly greater in comparison to patients receiving RV pacing (0.41 ± 0.13, P = 0.03). Patients with a LVEF ≤45% or with NYHA Class II/III symptoms appeared to have the most benefit.[44] Other studies have demonstrated an improvement in symptoms and LVEF in patients with reduced LVEF and chronic RV pacing with an upgrade to CRT.[45−47]

Unresolved Issues With Biventricular Pacing

The evidence supporting CRT in severe HF is compelling. However, device placement exerts a substantial ''placebo'' response of improved functional capacity and quality of life parameters in those randomized to the control group, and it is hampered by a significant nonresponder rate.[48,49] Most trials of CRT have excluded patients with atrial fibrillation. Thus the benefit of biventricular pacing in these patients remains unknown.

Should resynchronization be done in isolation or must it be accompanied by an ICD device? The findings in SCD-HeFT and COMPANION suggest that CRT therapy ideally should be accompanied by ICD placement in patients with NYHA III symptoms. When considering resynchronization in patients with more severe HF, the appropriateness of ICD implantation is uncertain. A recent analysis of ambulatory NYHA class IV patients in the COMPANION trial demonstrated a benefit of CRT and CRTD, but one year mortality remained high.[50]

Patients With a QRS Duration 120−150 ms. A substantial number of potential candidates for CRTs will have a QRS duration between 120 and 150 ms. Although such patients were entered in the clinical trials assessing efficacy of CRT, the average QRS duration was in the range of 160-170 ms and there are concerns that patients with moderate prolongation of the QRS interval may not derive the same benefit as those with more marked prolongation. Although CRT reduced the primary endpoint of time to death or all cause hospitalization compared to patients randomized to optimal medical treatment by 19% (P =.014) in the COMPANION Trial, a significant risk reduction was seen only in patients whose QRS was >168 ms.[17] Patients whose QRS was ≤147 ms demonstrated essentially no benefit of treatment, whereas CRT had an intermediate effect in the patients whose QRS duration fell in between these groups. In CARE-HF, there was a benefit of CRT in subjects with a QRS duration of 120-149 msec, but to be enrolled in the study these patients had to have two of three criteria for dyssynchrony (an aortic pre-ejection delay of more than 140 msec, an interventricular mechanical delay of more than 40 msec, or delayed activation of the posterolateral LV wall).[37]

There is no universally accepted method for measuring dyssynchrony, the methods may be operator or equipment dependent, and the strategy of using echocardiographic methods has not been tested against the well-studied strategy of using QRS duration. Therefore, caution should be applied when attempting to interpret echocardiographic measures of dyssynchrony in patients who meet standard criteria for CRT; in particular, caution should be applied when considering patients who do not meet criteria shown to benefit in randomized clinical trials (e.g. narrow QRS duration). Ongoing investigations will likely clarify use of imaging strategies for assessing dyssynchrony in the future.

Dual Chamber Pacemakers

Recommendation

9.12 The routine use of dual atrioventricular (AV) chamber pacemakers for HF in the absence of symptomatic bradycardia or high-grade AV block is not recommended. (Strength of Evidence = A)

Background

Abnormalities in AV conduction can contribute to a reduction in atrial contribution to ventricular filling and prolong the duration of mitral regurgitation into diastole. Restoration of these 2 hemodynamic phenomena provided the rationale for the potential benefits of AV synchronized pacing with optimal AV delay. Initial success showed a beneficial effect of cardiac pacing with a short AV delay in patients with HF.[51] Subsequent acute[52−54] and chronic studies[55−60] assessing the effect of shortening the AV delay in patients with impaired ventricular function showed mixed results. Three well-designed and randomized studies failed to show any consistent improvements in HF with shortening of the programmed AV delay. Another concluded that for patients with standard indications for ICD therapy, no indication for cardiac pacing, and an LVEF of 40% or less, dual-chamber pacing offers no clinical advantage over ventricular backup pacing and may be detrimental by increasing the combined end point of death or hospitalization for HF.[61]

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Section 10: Surgical Approaches to the Treatment of Heart Failure

Overview

Despite advances in medical management of heart failure (HF), there remain circumstances in which surgical procedures are the only or the best treatment option. Heart transplantation, the longest accepted surgical therapy, and procedures that (1) repair the heart, (2) reshape it, or (3) replace all or part of heart function are considered in this section of the guideline. Myocardial viability and revascularization are addressed in Section 13.

Recommendations

10.1 It is recommended that the decision to undertake surgical intervention for severe HF be made in light of functional status and prognosis based on severity of underlying HF and comorbid conditions. Procedures should be done at centers with demonstrable expertise and multidisciplinary medical and surgical teams experienced in the selection, care, and perioperative and long-term management of high risk patients with severe HF. (Strength of Evidence = C)

10.2 Evaluation for heart transplantation is recommended in selected patients with severe HF, debilitating refractory angina, or ventricular arrhythmia that cannot be controlled despite drug, device, or alternative surgical therapy. (Strength of Evidence = B)

Background

The short- and long-term success of heart transplantation is limited by shortage of donor organs. Only 2163 human heart transplants were performed in the United States in 2008, far below the 20,000 to 30,000 patients per year who could benefit from this therapy. Heart transplantation has demonstrated 1-year, 3-year and 5-year survival rates of 88%, 79% and 72%, respectively.[1] It thus provides a survival benefit in certain well-selected patients with an otherwise poor prognosis of survival at 1 year.[2]

Consideration of heart transplantation for HF patients should be based on a comprehensive multidisciplinary evaluation of risks. Referral for cardiac transplantation should be entertained for patients with considerable functional limitations from their cardiac disease despite optimal medical therapy.[3,4] Such patients typically are screened with a cardiopulmonary exercise test. If peak aerobic capacity is severely limited as indicated by a VO_2 max < 14 mL·kg·min or $\leq$55% of predicted for age and gender, transplantation may be considered.[5,6]

In the presence of obesity, particularly in women, traditional VO_2 max measurements may not stratify risk effectively. In such instances, adjusting VO_2 max for lean body mass may be preferable.[7] VO_2 max remains predictive of outcomes in patients taking beta blockers[8] but the level at which the risk-benefit ratio favors transplantation is reduced and appears closer to $\leq$12 mL·kg·min. Patients may undergo transplantation evaluation without formal cardiopulmonary exercise testing when contraindications to maximal exercise exist including refractory debilitating angina or ventricular arrhythmias.

The comprehensive cardiac transplant evaluation is designed to select patients in whom the procedure is likely to improve survival and quality of life while simultaneously identifying medical and psychosocial barriers to successful transplantation.[4] Thus, no single test can be used to define an appropriate candidate for transplantation. Widely accepted contraindications to cardiac transplantation include diabetes mellitus with widespread microvascular complications, irreversible chronic kidney disease or pulmonary hypertension, or other medical or psychosocial issues that would impact survival.[3] Increasingly more complex patients with multiorgan failure present for evaluation of cardiac transplantation. These patients either are deemed ''too high risk'' or alternatively may be offered multiorgan transplants including heart/kidney, heart/liver and heart/lung. Patients with a recent history of non-skin malignancy have a relative contraindication for heart transplantation, but should be evaluated in collaboration with oncology experts. Patients with a poor prognosis due to prior malignancy should be excluded from cardiac transplantation.[4]

Recommendation

10.3 Isolated mitral valve repair or replacement for severe mitral regurgitation secondary to ventricular dilatation in the presence of severe left ventricular (LV) systolic dysfunction is not generally recommended. (Strength of Evidence = C)

Background

There is little randomized clinical trial evidence to support the benefit of mitral valve repair, and the observational data are limited and conflicting. The pathophysiologic basis of mitral regurgitation results from ventricular dilatation with papillary muscle displacement and tethering of the chordae tendonae and mitral valve leaflets preventing normal coaptation. Papillary muscle ischemia or infarction, rupture of chordae tendonae and mitral leaflet pathology may also contribute to mitral regurgitation. Mitral regurgitation causes chronic volume overload of the left ventricle which worsens the LV dilation and has been associated with higher mortality.[9] Previous reports of excessive operative mortality with mitral valve replacement in patients with end-stage cardiomyopathy limited enthusiasm for surgical mitral valve correction in patients with severe ventricular dysfunction and mitral regurgitation.

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Recent data indicate that mitral valve repair, which preserves the subvalvular apparatus and cardiac function better than mitral valve replacement, can be performed with an acceptable perioperative mortality (<2% at 30 days) and good medium-term survival at highly experienced centers.[10] Mitral valve repair using an "undersized" annuloplasty ring effectively corrects mitral regurgitation,[11] improves symptoms and favorably remodels the left ventricle[12,13] in patients with systolic HF; however, a subsequent small randomized trial indicated no benefit of mitral valve repair in patients with mitral regurgitation because of ventricular dysfunction.[14] Development of risk stratification tools as well as controlled trials and registry data are needed before recommending this technique as an effective alternative to transplantation. A report by Mihaljevic and colleagues showed that over 5 years of follow up mortality in a cohort with ischemic mitral regurgitation was similar after coronary artery bypass graft surgery (CABG) with or without concomitant mitral valve repair.[15] This nonrandomized propensity matched cohort did demonstrate improved quality of life in the patients undergoing CABG with mitral valve repair.

Recommendation

10.4 Partial LV resection ("Batista procedure") is not recommended in nonischemic cardiomyopathy. (Strength of Evidence = B)

Background

There is no compelling evidence demonstrating the benefits of this procedure.[16]

Partial left ventriculectomy is associated with significant operative mortality and both short term and long term mortality due to arrhythmias and recurrent severe HF. A randomized trial of this operation has never been completed.

Recommendations

10.5 Patients awaiting heart transplantation who have become refractory to all means of medical circulatory support should be considered for a mechanical support device as a bridge to transplant. (Strength of Evidence = B)

10.6 Permanent mechanical assistance using an implantable assist device may be considered in highly selected patients with severe HF refractory to conventional therapy who are not candidates for heart transplantation, particularly those who cannot be weaned from intravenous inotropic support at an experienced HF center. (Strength of Evidence = B)

10.7 Patients with refractory HF and hemodynamic instability, and/or compromised end-organ function, with relative contraindications to cardiac transplantation or permanent mechanical circulatory assistance expected to improve with time or restoration of an improved hemodynamic profile should be considered for urgent mechanical circulatory support as a "bridge to decision." These patients should be referred to a center with expertise in the management of patients with advanced HF. (Strength of Evidence = C)

Background

Left ventricular assist devices (LVADs) can restore a normal cardiac output and promote physiologic recovery in patients with end-stage class D HF.[17-19] Mechanical circulatory support has been demonstrated to improve end-organ function in patients failing optimal medical therapy.[20,21] Resolution of medically refractory pulmonary hypertension[22,23] and improvements in functional capacity[24,25] have also been demonstrated.

Several devices have been approved as a means to bridge critically ill patients to transplantation. Implantable first generation LVADs (pulsatile pumps) that are approved for bridge-to-transplantation include the Novacor LVAS (Left Ventricular Assist System), the HeartMate XVE LVAS,[26] and the Cardiowest Total Artificial Heart.[27] Portable battery-powered devices allow patients to be discharged from the hospital, typically while waiting for heart transplant.[28] Development of transcutaneous energy sources that allow untethered circulatory support for prolonged periods of time are anticipated to improve quality of life and reduce the risk of infection in LVAD patients.

Newer generation LVADs that provide continuous flow are undergoing clinical evaluation. These devices offer the advantages of smaller size, a quiet operating mode, and enhanced durability. The recently published HeartMate II bridge-to-transplant trial demonstrated that 79% of patients were transplanted, alive on device support, actively listed for transplantation or had the device removed for recovery 6 months following enrollment.[29]

The use of mechanical circulatory support in selected patients who are not candidates for transplantation is an increasingly utilized strategy in advanced HF centers. The Randomized Evaluation of Mechanical Assistance for the Treatment of Congestive Heart Failure (REMATCH) trial randomized 129 patients with end-stage HF ineligible for cardiac transplantation to implantation of an LVAD or optimal medical management.[30] The primary end point was all-cause mortality. Patients enrolled had New York Heart Association (NYHA) class IV HF for at least 90 days despite optimal medical therapy. At 1 year, survival in the LVAD group was significantly greater than in the medical therapy group (52% vs 25%, $P = .001$). However, at 2 years, only 23% in the LVAD group were alive, compared with 8% in the medical group. Serious adverse events were more frequent in the LVAD group, predominately caused by infection, bleeding, neurologic dysfunction, and device malfunction. A subsequent analysis of the trial

data reported that the majority of the benefit in this trial was restricted to the group receiving or dependent on intravenous inotropic therapy at time of enrollment. Several new trials and the development of a national registry for LVAD patients will dramatically increase the knowledge base and provide important insights regarding the efficacy of mechanical circulatory support in the near future.[31]

Increasingly patients present with advanced HF that require urgent deployment of mechanical circulatory support to sustain life and or prevent or reverse end organ dysfunction. Often a thorough assessment cannot be completed to definitively determine if they patient is a suitable candidate for transplantation. Under these circumstances an LVAD should be implanted as a ''bridge to decision'' pending further assessment and determination of the best treatment plan in the post operative period. A prospective cohort of patients in the Interagency Registry for Mechanically Assisted Circulatory Support (INTERMACS) registry showed that strategy for treatment is dynamic and 20% of patients changed from various categories during the initial 3 months after device implant.[32]

Emerging Surgical Techniques

Infarct Exclusion Surgery. Primary indications for surgical treatment of LV aneurysm consist of LV failure, angina pectoris, thromboembolism, and tachyarrhythmias. It has been well recognized for decades that, after ventricular aneurysmectomy, patients can experience improved HF symptoms.[33] This concept recently has been expanded from dyskinetic (aneurysmal) ventricles to include akinetic ventricles, which previously were considered unlikely to improve following ventricular reconstruction. Linear aneurysmectomy has been widely performed as a standard procedure for post-infarction LV aneurysm. However, this technique remains unsatisfactory because LV distortion occurs postoperatively and an akinetic or dyskinetic area persists in the ventricular septum, resulting in limited improvement of cardiac function.[34] To overcome these problems, Dor and associates excluded all akinetic or dyskinetic myocardium from the left ventricle, including the septum, and placed a tight circumferential suture around the aneurysmal base to reduce the LV volume and return the LV contour to near normal (endoventricular circular patch plasty, or EVCPP). Recently, EVCPP has attracted interest as a treatment for post-infarction large akinetic scars. Dor's group has reported on the use of this technique on more than 750 patients.[35] Results were clinically satisfactory and in more than 90% of cases with ventricular aneurysm, the 1-year left ventricular ejection fraction was superior to the preoperative function. More recently, the same group reported on 44 patients treated with EVCPP with previous transmural anterior myocardial infarction.[36] They found that LV shape became more elliptical in systole than it was in diastole (eccentricity index closer to 1), but new onset mitral regurgitation occurred in 25% of patients.

A minor modification of the procedure described by Dor is referred to as the surgical anterior ventricular endocardial restoration (SAVER) operation. A large, multicenter prospective registry reported on 439 consecutive patients who received this operation with impressive medium-term survival. Based on this, the Surgical Treatment for Ischemic Heart Failure (STICH) trial, a large, National Institutes of Health-funded study of both CABG and ventricular reconstruction has been initiated. Still, the limited experience with this procedure and the concern that mitral valvular disease could be worsened leaves insufficient grounds for a recommendation of this technique at this time. The STICH trial demonstrated that surgical ventricular reconstruction did not offer significant benefit over coronary bypass surgery alone. The addition of surgical ventricular reconstruction to CABG reduced the LV volume, as compared with CABG alone, but this anatomical change was not associated with a reduction in the rate of death or hospitalization for cardiac causes.[37]

Passive Restraint. Another technique uses passive containment of the ventricles with a surgically placed epicardial prosthetic wrap constructed of either preformed knitted material[38] or nitinol.[39] The Acorn trial examined outcomes in 300 patients randomized to receive a cardiac restraint device or standard therapy.[40] More patients who received the cardiac support device achieved the primary end-point (alive, free of major cardiac procedures and $\geq$1 NYHA functional class improvement) than the patients treated with standard therapies, however there was no difference in mortality between groups. Early and sustained improvements in LV remodeling indices were also noted.[41] The Paracor HeartNet device has more limited observational data supporting its use, but preliminary studies suggest improvements in exercise performance, quality of life and cardiac structure with use of this device.[39]

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Section 11: Evaluation and Management of Patients with Heart Failure and Preserved Left Ventricular Ejection Fraction

Overview

A substantial number of patients with heart failure (HF) have preserved left ventricular ejection fraction (LVEF), variably defined as an LVEF >40%, >45%, or >50%.[1,2] When these patients have invasive or non-invasive evidence of abnormal diastolic function (either abnormal relaxation, filling or stiffness) they are said to have "diastolic HF".[3] Although the term "HF with normal LVEF" is often used to denote this group, because "normal" is variously defined, "HF with preserved LVEF" will be the active definition in this document. Few randomized clinical trials have been performed in this patient group, but appropriate treatment strategies have been proposed by the American College of Cardiology, American Heart Association, Canadian Society of Cardiology, and the European Society of Cardiology, and are proposed in this document by the Heart Failure Society of America.[4–10] Patients with a previously reduced LVEF whose LVEF has returned to normal with medical and/or device therapy should not be included in the classification of HF with preserved LVEF, but they should be treated as outlined in Section 7.

Pathophysiology. The left ventricle in HF with preserved LVEF may be characterized by LV hypertrophy,[11] concentric remodeling, increased extracellular matrix,[12] abnormal calcium handling, abnormal relaxation and filling and decreased diastolic distensibility.[6,13] Activation of the neurohormonal milieu, including the renin-angiotensin-aldosterone system (RAAS) and the sympathetic nervous system, is common in HF with and without preserved LVEF.[6]

Prevalence. In prospective studies, approximately 50% of the population of patients with HF has normal or near normal resting LVEF.[2,5,14–16] HF with preserved LVEF is particularly prevalent among the elderly, females, and patients with hypertension.[2,15,17,18] Among 4 prospective studies of HF with preserved LVEF, the average age range of patients was 73 to 79 years, and the percentage of females ranged from 61% to 76%.[2,14,19] However, neither age <70 years nor male gender excludes the diagnosis of HF with preserved LVEF.

Mortality and Morbidity. The mortality of patients with HF with preserved LVEF is considerable, and in the general population of unselected patients it may be comparable to mortality in patients with HF and reduced LVEF.[2,14,16] An analysis from the Framingham Heart Study showed that HF patients with preserved LVEF had lower 5 year mortality compared with those with reduced LVEF.[16] This difference was even more pronounced in the Candesartan in Heart Failure: Assessment of Reduction in Mortality and Morbidity (CHARM) study. However, in a study from Olmsted County, survival was similar for patients with HF and either reduced or preserved LVEF.[15]

This variability in relative clinical outcomes may reflect differences in criteria for the diagnosis of HF, the number of co-morbidities present, and the demographic and clinical composition of the populations studied. In the Olmstead County report, the mean age of the patients with HF with preserved LVEF was 77 ± 12 years.[15] In a recent review by the same investigators, mortality in HF with preserved LVEF was similar to that in patients with HF and reduced LVEF when patients were older than 65; among patients younger than 65, mortality was lower in those with preserved LVEF.[18]

HF with preserved LVEF is also associated with considerable morbidity. There is a 50% chance of re-hospitalization for HF in 6 months in patients with HF with preserved LVEF. A recent study comparing patients with preserved or reduced LVEF found similar rates of hospital readmissions, HF readmissions, and functional decline.[2]

Women make up a majority of patients with HF with preserved LVEF.[14,16,20] Most studies have shown no difference in survival by gender, but in the Digitalis Investigation Group (DIG) study [21] and one other study,[16] female gender was associated with improved survival.

An analysis of the Coronary Artery Surgery Study registry showed that the presence of coronary artery disease (CAD) was an adverse factor for survival in patients with HF and LVEF >45%.[22] A review of the available literature in 2002 showed that the prevalence of CAD in patients with HF and preserved LVEF ranged widely from 0% to 67%, but is clearly less than the prevalence in HF and a reduced LVEF.[6]

Recommendation

11.1 Careful attention to differential diagnosis is recommended in patients with HF and preserved LVEF to distinguish among a variety of cardiac disorders, because treatments may differ. These various entities may be distinguished based on echocardiography, electrocardiography, and stress imaging (via exercise or pharmacologic means, using myocardial perfusion or echocardiographic imaging) and cardiac catheterization. See Figures 11.1, 11.2, and 11.3 for guidance to a differential diagnosis. (Strength of Evidence = C)

Background

Diagnosis. The clinical diagnosis of HF depends on the presence of commonly accepted signs and symptoms (Fig. 11.1). Preserved LVEF may be shown by quantifying LVEF and LV volumes or dimensions through imaging techniques such as echocardiography, radionuclide ventriculography, contrast ventriculography, or cardiac

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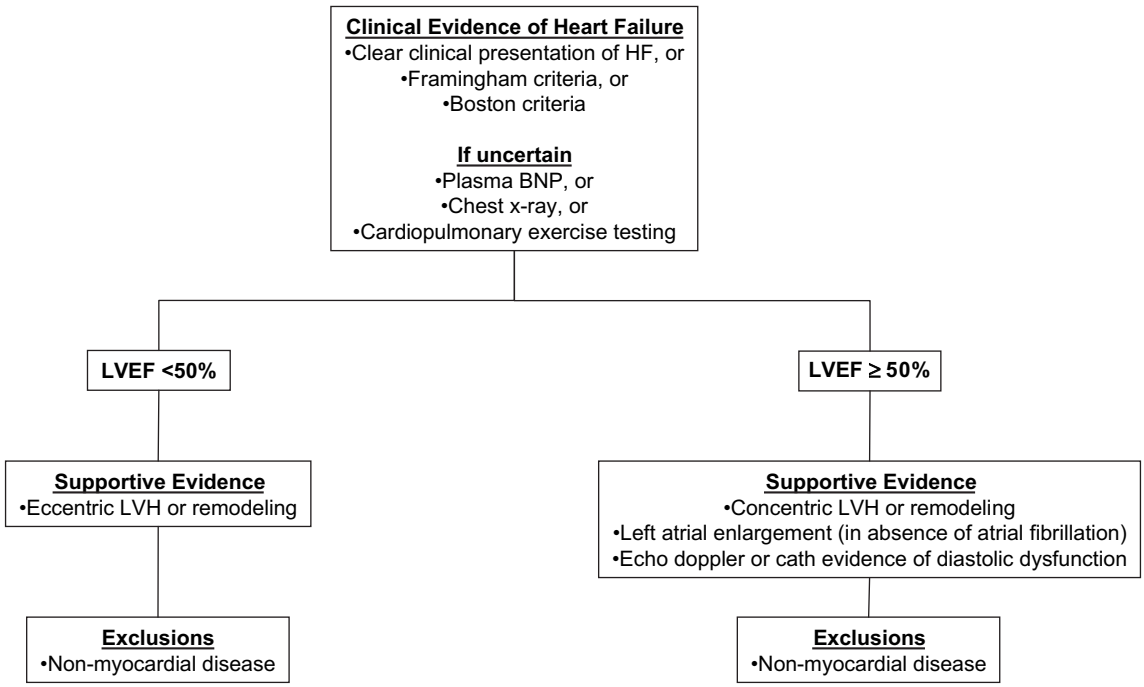


Adapted from Yturralde FR et al. *Prog Cardiovasc Dis* 2005;47:314-319.

Fig. 11.1. Diagnostic Criteria: HF with Reduced Versus HF with Preserved EF.

magnetic resonance imaging. Among these, echocardiography is the most commonly used and has several advantages, including availability and the ability to provide information about LV wall thickness, filling patterns, cardiac anatomy, and valvular function.

Confirmation of increased LV diastolic filling pressure by documenting elevation of B-type natriuretic peptide (BNP or NT-proBNP) may be useful when dyspnea may be due to noncardiac causes.[23] Increased BNP or NT-proBNP may identify patients with elevation of the LV diastolic pressures, but does not differentiate patients with preserved versus reduced LVEF.[24] HF with reduced LVEF tends to be associated with greater elevation of BNP than does HF with preserved LVEF, but BNP is above normal in both categories of HF, except in the obese patient, where BNP or NT-proBNP may be falsely low.[25] In HF with preserved LVEF, there is some overlap with the normal range.[23,24,26]

Differential Diagnosis. The causes of HF with either preserved or reduced LVEF are similar as shown in Figure 11.2. A diagnostic algorithm for patients with HF and preserved LVEF is outlined in Figure 11.3. LV hypertrophy (LVH) or concentric remodeling diagnosed by echocardiography or electrocardiography, is commonly present in patients with HF with preserved LVEF. Doppler echocardiography frequently demonstrates abnormalities in LV diastolic function.

The echocardiogram is more sensitive than the electrocardiogram for the diagnosis of LVH.[27] In addition to chronic systemic hypertension, LVH may be due to other causes of LV pressure overload, such as aortic stenosis or aortic coarctation. Detecting LVH in the absence of an obvious cause for LV pressure overload supports the diagnosis of hypertrophic cardiomyopathy. This condition is usually regional (eg, septal, apical), but may be global. It is usually familial and genetically mediated.[28,29] Increased wall thickness by echocardiography, coupled with low voltage on the electrocardiogram, strongly supports the diagnosis of an infiltrative cardiomyopathy. Among the most common infiltrative disorders is amyloidosis,[30] a disorder with a very poor prognosis.[31] In addition to low voltage, pseudo-infarction Q waves may be present. In the absence of hypertrophy, other infiltrative processes include sarcoidosis and Gaucher's disease. Sarcoid nodules in the myocardium rarely cause LV restrictive physiology, but pulmonary sarcoidosis may commonly cause pulmonary hypertension and right-sided HF.[32]

Less common storage disorders include hemochromatosis. Rare disorders include Fabry disease and glycogen storage diseases. Hemochromatosis has several etiologies (familial, idiopathic, and acquired) and is manifested primarily as a dilated cardiomyopathy with reduced systolic performance, but occasionally as a non-dilated, restrictive cardiomyopathy.[33] Fabry disease may be associated initially with normal LV mass, but later with hypertrophy. Restrictive disorders are rare, and may be associated with either LVH or normal LV mass.[34] Endomyocardial disorders include endomyocardial fibrosis (usually in tropical climates); the hypereosinophilic syndrome, which may or may not be related to endomyocardial fibrosis; and carcinoid.

In the absence of aortic or mitral regurgitation, LV volume overload denotes a high cardiac output because of ventricular

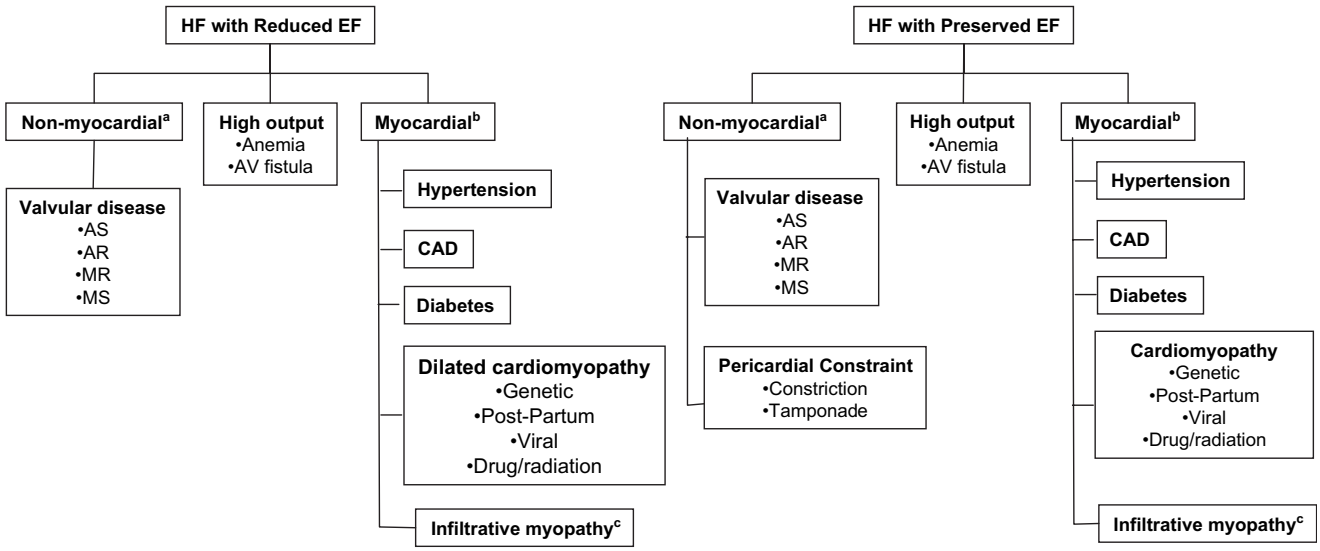


Fig. 11.2. Etiology of HF with Reduced Versus HF with Preserved EF.

septal defect, patent ductus arteriosus or other arteriovenous shunt, chronic anemia, thyrotoxicosis, or chronic liver disease.

It is essential to clarify the diagnosis of pericardial disorders with constrictive physiology versus restrictive disorders. In the absence of substantial pericardial fluid, the diagnosis of pericardial disease may require invasive hemodynamics, computerized tomography, or magnetic resonance imaging to identify pericardial thickening.[35]

In contrast to restrictive and infiltrative cardiomyopathies and to pericardial disease, ischemic heart disease with transient LV dysfunction is much more common. It is considered here and in other sections, particularly Section 13.

Right ventricular (RV) dysfunction is most commonly caused by LV dysfunction. In such conditions, there is pulmonary hypertension. Other causes of pulmonary hypertension, such as pulmonary thromboembolic disorders and intrinsic lung disease, may also precipitate RV dysfunction. Occasionally severe RV dysfunction may follow RV infarction. Occasionally chronic RV dysfunction can cause LV dysfunction resulting from ventricular interaction, a situation in which RV pressure-volume overload may deform and displace the interventricular septum toward the LV, increasing LV diastolic pressure even as LV volume remains constant or decreases. Such conditions reduce LV compliance.

In summary, there is a broad differential diagnosis of all HF patients. This is also true in HF with preserved LVEF and must be kept in mind during the initial evaluation of such patients. Hypertensive LVH is the most common cause of HF with preserved LVEF. However, CAD and diabetes mellitus are also common disease processes associated with the development of HF with preserved LVEF. In analyzing HF in such patients, most emphasis has centered on assessment of LV and LA structural changes and changes in LV diastolic function.

Recommendation

11.2 Evaluation for ischemic heart disease and inducible myocardial ischemia is recommended in patients with HF and preserved LVEF (see Section 13). (Strength of Evidence = C)

Background

Section 13 provides a detailed approach to the diagnosis of ischemic heart disease in patients with HF by noninvasive stress imaging and by cardiac catheterization. Ischemic mitral regurgitation, acute or chronic, may aggravate HF with normal systolic performance.

Recommendations

11.3 Blood pressure monitoring is recommended in patients with HF and preserved LVEF (Section 14, Recommendation 14.1). (Strength of Evidence = C)

11.4 Counseling on the use of a low-sodium diet (Section 6) is recommended for all patients with HF, including those with preserved LVEF. (Strength of Evidence = C)

11.5 Diuretic treatment is recommended in all patients with HF and clinical evidence of volume overload, including those with preserved LVEF. Treatment may begin with either a thiazide or loop diuretic.

In more severe volume overload or if response to a thiazide is inadequate, treatment with a loop diuretic should be implemented. Excessive diuresis, which may lead to orthostatic changes in blood pressure and worsening renal function, should be avoided. (Strength of Evidence = C)

Background

In conditions with LVH, restrictive or constrictive physiology, a small decrease in intravascular volume may be associated with significant reduction in LV preload, resulting in decreased cardiac output. Orthostatic changes and prerenal azotemia provide evidence for excessive preload reduction.[6] Acutely, in addition to diuretics, nitrates may have a role in diminishing pulmonary venous pressure and clinical congestion. Chronically, the effects may be similar, but one must be alert to the possibility of excess reduction in LV preload.

Recommendation

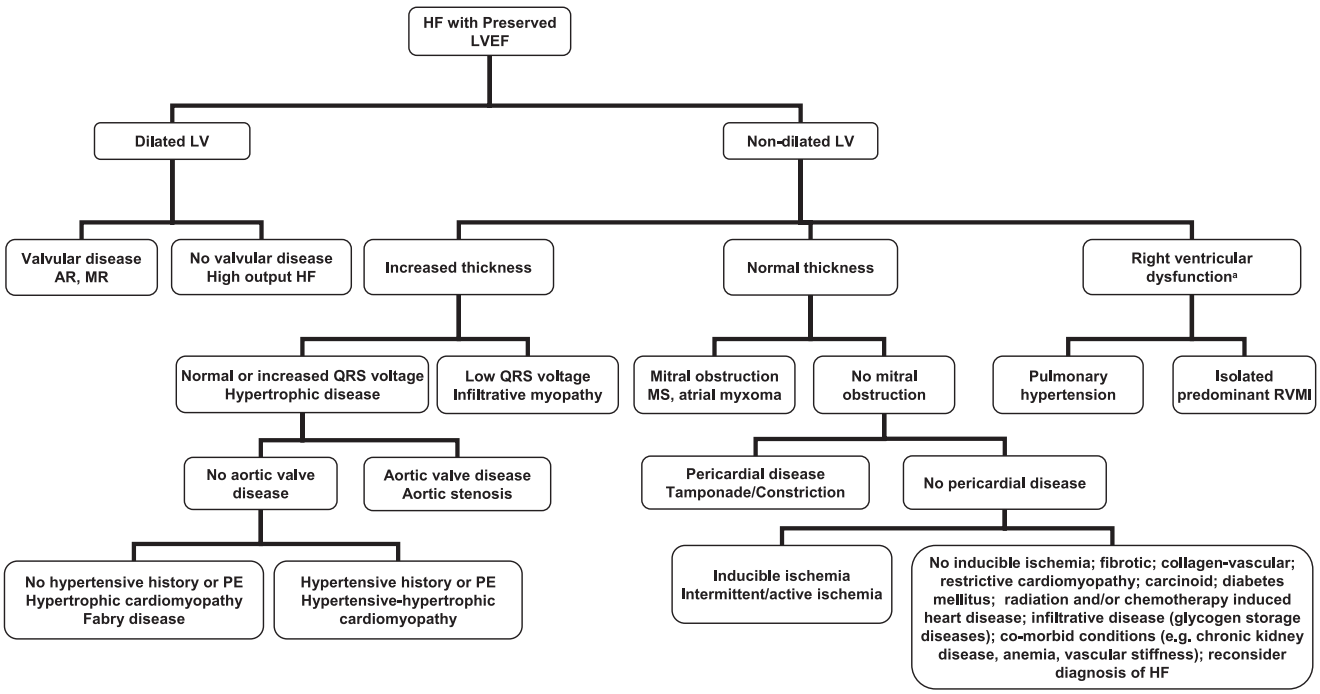
11.6 In the absence of other specific indications for these drugs, angiotensin receptor blockers (ARBs) or angiotensin converting enzyme (ACE) inhibitors may be considered in patients with HF and preserved LVEF.

- **ARBs (Strength of Evidence = C)**
- **ACE inhibitors (Strength of Evidence = C)**

Background

A trial of the ARB, candesartan, in patients with HF and preserved LVEF showed a trend toward reduction in the primary endpoint of cardiovascular death or hospitalization (unadjusted hazard ratio 0.89, CI 0.77-1.03, $P = .118$; adjusted hazard ratio 0.86, CI 0.74-1.00, $P = .051$).[36] At enrollment, approximately 20% of patients were receiving ACE inhibitors and 55% were receiving beta adrenergic blocking drugs. There was no subset analysis of the combination of these drugs in these specific patients, but the candesartan group showed a reduction in both hospitalizations and blood pressure.

The Irbesartan in Heart Failure with Preserved Ejection Fraction (I-PRESERVE) study enrolled 4128 patients who were at least 60 years of age and had New York Heart Association class II, III, or IV HF and a LVEF of at least 45% and randomly assigned them to receive 300 mg of irbesartan or placebo per day.[37] The primary composite outcome was death from any cause or hospitalization for a cardiovascular cause (HF, myocardial infarction, unstable angina, arrhythmia, or stroke). Secondary outcomes included death from HF or hospitalization for HF, death from any cause and from cardiovascular causes, and quality of life. During a mean follow-up of 49.5 months, the primary outcome occurred in 742 patients in the irbesartan group and 763 in the placebo group. Primary event rates in the irbesartan and placebo groups were 100.4 and 105.4 per 1000 patient-



LVEF = left ventricular ejection fraction; HF = heart failure; QRS = electrocardiographic ventricular depolarization; AR = aortic Regurgitation; MR = mitral regurgitation; MS = mitral stenosis; RVMI = right ventricular myocardial infarction; PE = pulmonary embolism

[a]Some patients with right ventricular dysfunction have LV dysfunction due to ventricular interaction

Fig. 11.3. Diagnostic Algorithm for Heart Failure with Preserved LVEF.

years, respectively (hazard ratio, 0.95; 95% confidence interval [CI], 0.86 to 1.05; P = 0.35).Overall rates of death were 52.6 and 52.3 per 1000 patient-years, respectively (hazard ratio, 1.00; 95% CI, 0.88 to 1.14; P = 0.98). Rates of hospitalization for cardiovascular causes that contributed to the primary outcome were 70.6 and 74.3 per 1000 patient-years, respectively (hazard ratio, 0.95; 95% CI, 0.85 to 1.08; P = 0.44). There were no significant differences in the other prespecified outcomes. Irbesartan did not improve the outcomes of patients with HF and preserved LVEF.

Recommendation

11.7 ACE inhibitors should be considered in all patients with HF and preserved LVEF who have symptomatic atherosclerotic cardiovascular disease or diabetes and one additional risk factor. (Strength of Evidence = C)

In patients who meet these criteria but are intolerant to ACE inhibitors, ARBs should be considered. (Strength of Evidence = C)

Studies supporting the use of ACE inhibitors in patients with HF and preserved LVEF did not enroll patients with known HF. A secondary endpoint of the Heart Outcomes Prevention Evaluation (HOPE) trial was progression to HF in the following high risk patients: those older than age 55 years with either documented vascular disease or multiple cardiac risk factors, one of which was diabetes.[38] In this randomized study, 9297 patients received double-blind placebo or ramipril 10 mg daily and were followed for 4.5 years. The annual risk for development of HF was approximately 2.5%, which was reduced by 23% with the ACE inhibitor. The risk reduction was independent of multiple covariates. The presence of a subsequent MI during the study increased the risk of developing HF more than eightfold. Treatment with ramipril was associated with a 33% reduction in the development of HF in those with a baseline systolic pressure above the median of 139 mm Hg versus only 9% in those whose systolic blood pressure was below the median *(P* = .024).

The European Trial on Reduction of Cardiac Events with Perindopril in Stable Coronary Artery Disease (EUROPA) studied high dose ACE inhibitor therapy versus placebo in patients older than age 18 with documented CAD.[39] A mean follow-up of 4.2 years showed that perindopril reduced total mortality by 14% (from 6.9% to 6.1%), recurrent MI by 22% (6.2% to 4.8%), and hospital admission for HF by 39%. All findings were statistically significant, were consistent in all predefined subgroups, were independent of coexistent beta blocker therapy, and were seen in the setting of aggressive treatment of vascular disease, as determined by the high rate of antiplatelet (92%), antilipid (58%), and beta blocker (62%) usage.

Recommendation

11.8 Beta blocker treatment is recommended in patients with HF and preserved LVEF who have:

- **Prior myocardial infarction (Strength of Evidence = A)**
- **Hypertension (see Section 14) (Strength of Evidence = B)**
- **Atrial fibrillation requiring control of ventricular rate (Strength of Evidence = B)**

Background

No large-scale studies to date have demonstrated improvement in clinical outcomes from beta blockers specifically in patients with HF and preserved LVEF. However, as with ACE inhibitors, large subsets of this population fall into one or another category for which beta blockers have either proven beneficial or are highly likely to achieve clinical benefit.

In failing hearts, rapid rates are associated with progressively reduced contractile force and increased resting tension. The increased resting tension is related to incomplete relaxation due to incomplete reuptake of calcium to storage sites in the sarcoplasmic reticulum.[13] In a noninvasive study of hypertrophic cardiomyopathy, beta adrenergic blocking drugs prolonged diastolic filling time, suggesting better LV filling.[40] In the presence of CAD, tachycardia is associated with a prompt increase in LV diastolic pressure when associated with ischemia.[41] Thus reducing the heart rate with beta adrenergic blocking drugs should be beneficial for LV filling and a reduction in the LV end-diastolic pressure. Furthermore, retrospective studies have suggested substantial benefit of adequate rate control on systolic function in patients with atrial fibrillation with a rapid ventricular response.[42,43] Patients with sinus tachycardia may benefit from a reduction in heart rate; however, because the tachycardia may reflect an inability to increase stroke volume, care must be taken when using beta blockade.

The Study of the Effects of Nebivolol Intervention on Outcomes and Rehospitalization in Seniors with Heart Failure (SENIORS) study was a randomized trial in 2128 patients ≥70 years with a history of HF (a hospitalization for HF in the last year or an LVEF ≤35%). The primary endpoint of all-cause mortality or cardiovascular hospitalizations was reduced with nebivolol from 35.3% to 31.1% (HR = 0.86, 95% CI = 0.74-0.99, p = 0.039).[44] Thirty-five percent of patients in SENIORS had an LVEF of >35% and there was no significant difference in the effect of nebivolol between the group with an LVEF >35% and that with an LVEF ≤35%.[45] However, more than half of subjects with an LVEF >35% had an LVEF of 35-50%, leaving a small number of subjects with preserved LVEF. [44] In a study of ventricular remodeling comparing Chinese patients with HF and an LVEF <40%, 40-55%, or > 55%, the cohort with a mildly decreased LVEF had eccentrically enlarged ventricles with evidence of remodeling (rightward shifted end-diastolic pressure-volume relation) and decreased chamber contractility (downward shifted end-systolic pressure-volume relation) most comparable to subjects with overt systolic HF.[46] Studies comparing patients with HF and mildly reduced LVEF also suggest

that clinical features of patients with mildly reduced LVEF are more comparable to patients with an LVEF < 40 than in those with a preserved LVEF.[47,48] Thus, data are inadequate to recommend beta-blockers for most patients with HF and a preserved LVEF (LVEF >55%) in the absence of prior MI, hypertension, or atrial fibrillation requiring adequate rate control.

Recommendation

11.9 Calcium channel blockers should be considered in patients with HF and preserved LVEF and:
- **Atrial fibrillation requiring control of ventricular rate and intolerance to beta blockers. In these patients, diltiazem or verapamil should be considered. (Strength of Evidence = C)**
- **Symptom-limiting angina. (Strength of Evidence = A)**
- **Hypertension. (Strength of Evidence = C)**

Background

Although controlled clinical trial data are lacking, several properties of the calcium channel blocking drugs (eg, verapamil, diltiazem), suggest they may benefit patients with HF and preserved LVEF. Beyond these circumstances, calcium channel blockers are not routinely recommended, despite small studies showing hemodynamic benefit in select patients.

An important effect of these drugs is slowing heart rate. This effect should enhance calcium removal from the myocyte and calcium reuptake in the sarcoplasmic reticulum.[6,13,49] This should lower end-diastolic pressure[49] and improve passive ventricular filling.[50] Improved passive ventricular filling is associated with long-term improvement in exercise capacity in patients with hypertrophic obstructive cardiomyopathy, a clinical condition which, like HF with preserved LVEF, may be associated with significant abnormalities in myocardial relaxation.[50] Numerous studies have shown benefit from verapamil or diltiazem in chronic stable angina pectoris, although the patients likely did not have HF with preserved LVEF.[51] Verapamil has been shown to acutely reduce arterial stiffness in elderly normal subjects. The improvement is due to improved arterioventricular interaction, and this reduction in arterial stiffness has been related to improved exercise performance.[52]

Recommendation

11.10 Measures to restore and maintain sinus rhythm may be considered in patients who have symptomatic atrial flutter-fibrillation and preserved LVEF, but this decision should be individualized. (Strength of Evidence = C)

Background

In patients with atrial fibrillation or flutter who remain symptomatic after adequate rate control, it is reasonable to consider restoration of sinus rhythm. Because studies comparing rhythm control to rate control in patients with atrial fibrillation have generally excluded symptomatic patients, there are no randomized clinical trials for guidance. Nevertheless, retrospective evaluation of studies of patients with HF suggest that in the subset of patients with atrial fibrillation both amiodarone and dofetilide increased conversion to sinus rhythm and maintenance of sinus rhythm.[53–55]

These trials also demonstrated the safety of these drugs in patients with HF. Early experience suggests that catheter ablation of atrial fibrillation may also be considered in patients with HF to improve symptoms.[56]

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Section 12: Evaluation and Management of Patients with Acute Decompensated Heart Failure

Overview

Acute decompensated heart failure (ADHF) has emerged as a major public health problem over the past 2 decades.[1,2] Heart failure (HF) is the leading cause of hospitalization in patients older than 65 years of age. In-hospital mortality is excessive and readmission is disturbingly common, despite advances in pharmacotherapy and device therapy for HF.[3,4] The large direct costs associated with caring for the 5 million Americans who have chronic HF are largely attributable to hospitalization.[5]

Data from several studies have refined our understanding of the clinical characteristics of patients hospitalized with worsening HF.[2,4–6] These studies demonstrate that the majority of patients hospitalized with HF have evidence of systemic hypertension on admission and commonly have preserved left ventricular ejection fraction (LVEF). Most hospitalized patients have significant volume overload, and congestive symptoms predominate. Patients with severely impaired systolic function, reduced blood pressure, and symptoms from poor end-organ perfusion are in the distinct minority. Natural history studies have shown that ADHF represents a period of high risk for patients, during which their likelihood of death and rehospitalization is significantly greater than for a comparable period of chronic, but stable HF.[6]

The clinical classification of patients with ADHF continues to evolve and reflects ongoing changes in our understanding of the pathophysiology of this syndrome.[7] Worsening renal function, persistent neurohormonal activation, and progressive deterioration in myocardial function all seem to play a role. Decompensation also commonly occurs without a fundamental worsening of underlying cardiac structure or function. Failure to adhere to prescribed medications related to inadequate financial resources, poor adherence, and lack of education or an inadequate medical regimen may lead to hospitalization without a worsening of underlying circulatory function.

There is a paucity of controlled clinical trial data to define optimal treatment for patients with acute HF. The few trials have focused primarily on symptom relief, not outcomes, and have mainly enrolled patients with reduced LVEF who were not hypertensive. Clinical studies to determine the best care processes to achieve the multiple goals for patients admitted with ADHF are lacking. The recommendations in this section address the common therapeutic dilemmas associated with the broad group of patients with ADHF using the best available evidence from clinical research and consensus expert opinion.

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Diagnosis

Recommendation

12.1 The diagnosis of acute decompensated HF should be based primarily on signs and symptoms. (Strength of Evidence = C)

When the diagnosis is uncertain, determination of plasma B-type natriuretic peptide (BNP) or N-terminal pro-B-type natriuretic peptide (NT-proBNP) concentration is recommended in patients being evaluated for dyspnea who have signs and symptoms compatible with HF. (Strength of Evidence = A)

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, and with the knowledge of cardiac and noncardiac factors that can raise or lower natriuretic peptide levels.

Background

Signs and Symptoms. The major symptoms of ADHF, shortness of breath, congestion, and fatigue, are not specific for cardiac and circulatory failure.[8] They may be caused by other conditions which mimic HF, complicating the identification of patients with this syndrome. Various forms of pulmonary disease, including pneumonia, reactive airway disease and pulmonary embolus, may be especially difficult to differentiate clinically from HF.[9]

Diagnostic Utility of Natriuretic Peptides. Two forms of natriuretic peptides, BNP and NT-proBNP, have been studied as aids to establish the diagnosis, estimate prognosis and monitor the response to therapy of patients with ADHF.[10]

Measurement of these peptides has been proposed in cases where the diagnosis of HF is uncertain. A large, multicenter investigation, The Breathing Not Properly Study provides important evidence supporting the clinical utility of plasma BNP in the assessment of patients presenting with possible HF.[11,12] This study evaluated 1586 patients seen in the emergency department with the complaint of acute dyspnea who had prospective determination of BNP by bedside assay. Patients were assigned a probability of HF by physicians in the emergency department who were blinded to the results of the BNP assay. The final determination of whether or not HF was present was based on a review of the clinical data by 2 cardiologists also blinded to the BNP assay results. The sensitivity and specificity of BNP measurements for the diagnosis of HF were compared with the accuracy of an assessment based on standard clinical examination.

The diagnostic accuracy of BNP, using a cutoff value of 100 pg/mL, was 83% relative to the assessment made by the independent cardiologists, whereas the negative predictive value of BNP for HF when levels were <50 pg/mL was 96%. As expected, measurement of BNP appeared to

be most useful in patients with an intermediate probability of HF. In these patients, a BNP cutoff value of 100 pg/mL resulted in the correct classification 74% of the time. BNP was found to be predictive of HF when left ventricular (LV) function was depressed or preserved.[13] Although BNP levels were lower in patients with HF associated with preserved LVEF, the cutoff value of 100 pg/mL still had a sensitivity of 86% and a negative predictive value of 96%. BNP levels increase with age, more so in older women, so that cutoff of 100 pg/mL may not provide the same degree of specificity for the diagnosis of HF, especially in elderly women with dyspnea.[14,15]

The clinical utility of NT-proBNP in the diagnosis of HF was reported in the N-terminal Pro-BNP Investigation of Dyspnea in the Emergency Department (PRIDE) study. This study used NT-proBNP measurements in the emergency department to rule out acute HF in 600 patients who presented with dyspnea.[16] NT-proBNP results were correlated with a clinical diagnosis of acute HF as determined by study physicians blinded to these measurements. The median NT-proBNP level among the 209 patients who had acute HF (35%) was 4054 versus 131 pg/mL among 390 patients who did not (65%, $P < .001$). NT-proBNP levels increase with age so that the study investigators recommend NT-proBNP cut points of >450 pg/mL for patients younger than 50 years of age and >900 pg/mL for patients age 50 years or older, both of which were highly sensitive and specific for HF in this study. For patients 75 years or older, 1800 pg/mL is the recommended cutpoint for NT-proBNP.[17,18]

Prognostic Role of Natriuretic Peptides. Although baseline BNP levels may correlate only modestly with pulmonary capillary wedge pressure (PCWP), changes in PCWP do correlate directly with changes in BNP concentration during hospitalization.[19,20] The predischarge BNP after treatment for acute HF appears to predict patients at risk of early readmission or death following hospitalization for HF.[21,22] Although specific discharge cutoff values are still being defined, patients whose BNP increases during hospitalization are at very high risk, as are patients with levels >700 pg/mL at discharge. Patients with levels <350 pg/mL at discharge appear to be at relatively low risk of readmission and death after discharge. Two recent studies have demonstrated that discharge BNP and change in BNP from admission to discharge provide independent predictive value for poor outcomes after an episode of ADHF.[22,23]

Triage Value of Natriuretic Peptides. The value of BNP determination in the triage of patients seen in the emergency department has been evaluated in a prospective, randomized, controlled, single-blind study in which 452 patients presenting with acute dyspnea were randomized to assessment with routine clinical evaluation or routine clinical evaluation plus the measurement of BNP. The diagnosis of HF was considered ruled out when BNP levels were <100 pg/mL, whereas levels of >500 pg/mL were considered diagnostic of ADHF.

Fewer patients were hospitalized or admitted to intensive care units in the BNP aided group compared with those evaluated by standard clinical evaluation alone. The median time to discharge was 8 days in the group with BNP measured versus 11 days in the control group ($P = .001$). Although the data on outcomes from this study are not definitive and the hospital lengths of stay are not reflective of practice patterns in the United States, making generalizability problematic, they do not suggest that triage using BNP resulted in the under-treatment of patients truly at risk. The readmission rate for HF was similar in the 2 study groups and the mortality rate, while not reduced statistically, was lower in those patients with BNP determined. Larger randomized trials of this strategy are needed to assess the impact of this approach on adverse outcomes associated with admission for ADHF.

Use of Natriuretic Peptides to Guide Therapy. A small number of studies have evaluated the use of BNP or NT-proBNP to guide HF therapy. In the initial study, Troughton et al[24] randomized 69 patients with symptomatic HF and LVEF <40% to a clinically guided treatment group and a group for whom therapy was increased to drive the aminoterminal portion of BNP (N-BNP) level to <200 pg/mL. In the N-BNP guided group there were fewer total cardiovascular events (death, hospital admission, or HF decompensation than in the clinical group (19 *vs* 54, p=0·02). At 6 months, 27% of patients in the N-BNP group and 53% in the clinical group had experienced a first cardiovascular event (p=0·034). Changes in LV function, quality of life, renal function, and adverse events were similar in both groups. In the Systolic Heart Failure Treatment Supported by BNP (STARS-BNP) study[25] 220 patients with New York Heart Association (NYHA) Class II-III HF symptoms on evidence-based medical therapy with angiotensin converting enzyme (ACE) inhibitors and beta blockers were randomized to a clinical care group and a group for whom the goal was a BNP of <100 pg/mL. The primary endpoint of HF hospitalization or HF death was significantly lower in the BNP group (24% vs 52%, p, 0.001). All-cause hospital stays were not different in the two groups (60 in the control group vs 52 in the BNP group) while HF hospital stays were significantly different favoring the BNP group (48 in control group vs 22 in BNP group, p< 0.0001) Thus there were 30 non-HF hospital stays in the BNP group vs only 12 in the control group raising the concern that targeting therapy to BNP might lead to hospitalizations for hypotension, renal insufficiency, or hyperkalemia although the specific reasons for non-HF hospitalizations were not mentioned.

The randomized controlled multicenter Trial of Intensified vs Standard Medical Therapy in Elderly Patients With Congestive Heart Failure (TIME-CHF) enrolled 499 patients aged 60 years or older with systolic HF (LVEF ≤45%), NYHA class of II or greater, prior hospitalization

for HF within 1 year, and N-terminal BNP level of 2 or more times the upper limit of normal.[26] The primary endpoints were survival free of all cause hospitalizations and quality of life. There were similar rates of survival free of all-cause hospitalizations (41% vs 40%, respectively; hazard ratio [HR], 0.91 [95% CI, 0.72-1.14]; $P=.39$) in both groups over 18 months of follow-up. Quality-of life metrics improved but these improvements were similar in both the N-terminal BNP–guided and symptom-guided strategies. Survival free of hospitalization for HF, a secondary end point, was higher among those in the N-terminal BNP–guided group (72% vs 62%, respectively; HR, 0.68 [95% CI, 0.50-0.92]; $P=.01$).

The ''Can Pro-Brain-Natriuretic Peptide Guided Therapy of Chronic Heart Failure Improve Heart Failure Morbidity and Mortality?'' (PRIMA) study presented at the American College of Cardiology 2009 Scientific Sessions enrolled 345 HF patients who were hospitalized with elevated NT-proBNP levels ($\geq$1700 pg/mL).[27] After NT-proBNP levels dropped by more than 10% (to 850 pg/mL or less), patients were randomized to receive NT-proBNP-guided treatment (n=174) or clinically guided treatment (n=171). Serum levels of NT-proBNP were measured at discharge and again at the first follow-up period (two weeks post-discharge). The lesser of the two values was deemed the target value. If the NT-proBNP levels in patients in the guided-treatment group showed any increase at any subsequent follow-up, more intensive heart-failure therapy was immediately instituted. At a median follow-up of 702 days (range 488-730) there was a small but non-significant increase in the trial's primary end point—number of days alive outside the hospital—among patients in the NT-proBNP-guided group. Survival free of HF hospitalizations, a secondary endpoint, was significantly lower in the NT-proBNP group.

Based on all these results, it is not yet possible to recommend the use of natriuretic peptides to guide HF therapy, in either the outpatient or inpatient setting. Larger trials using HF hospitalization and mortality are being planned.

Limitations of Natriuretic Peptides. There are limitations concerning the utility of natriuretic peptides in the diagnosis of HF that need to be considered to gain maximum benefit from this testing.[28] Some patients with obvious ADHF by clinical criteria may not have BNP levels typically considered to be diagnostic. In contrast, there may be patients, especially those with chronic LV systolic function, who have persistently elevated BNP levels despite clinical compensation and adequate volume status.[29] Single measurements of BNP or NT-Pro BNP may not correlate well with measures of PCWP in patients in the intensive care unit, especially in patients with renal dysfunction.[13] In addition, the biologic variability of the assays for BNP is high making interpretation of day-to-day measurements problematic.[30]

Interpretation of natriuretic hormone levels can be problematic in patients with pulmonary disease. BNP and NT-proBNP may be increased in patients with pulmonary embolus or cor pulmonale resulting from right HF in the absence of congestion.[31] Some patients with HF without LV dysfunction may require treatment for peripheral edema despite having low BNP levels, indicating that BNP determination cannot always identify patients who need diuretic therapy. Patients with pulmonary disease may have concomitant LV dysfunction which may become more symptomatic during a primary respiratory illness, further complicating the interpretation of BNP levels.

The ranges of BNP for patients with and without a final diagnosis of HF overlap, which makes the test potentially less valuable in an individual patient with intermediate levels of BNP. Because many conditions can increase BNP levels, low values of BNP are most useful because they make the diagnosis of decompensated HF very unlikely as an explanation for dyspnea. Decision analysis indicates that BNP testing is generally most useful in patients who have an intermediate probability of HF. BNP levels rarely alter the diagnosis in patients who are very likely or unlikely to have HF based on usual clinical evaluation. ADHF remains a clinical phenomenon of symptoms due to circulatory dysfunction whose identification as yet cannot be reduced to a single laboratory measurement. Results of BNP testing must be interpreted in the context of the overall clinical evaluation, and such testing must augment rather than supersede careful clinical reasoning.[32]

Hospital Admission

Recommendation

12.2 Hospital admission is recommended for patients presenting with ADHF when the clinical circumstances listed in Table 12.1(a) are present. Patients presenting with ADHF should be considered for hospital admission when the clinical circumstances listed in Table 12.1(b) are present. (Strength of Evidence = C)

Background

The clinical characteristics detailed in this recommendation serve as a guide to determine which patients presenting with worsening HF require hospitalization. These criteria delineate severe symptoms that necessitate rapid relief; situations where outpatient therapy, typically with oral medications, is unlikely to be effective; and instances in which deterioration in the patient's clinical condition requires more intense monitoring than can be accomplished in an outpatient setting. In addition, some patients with decompensated HF require invasive diagnostic procedures, coronary intervention or surgical treatments that necessitate hospitalization. The application of these guidelines for admission should take into account the level of outpatient support and services available, the response to therapy in the emergency department, and the therapeutic goals for each patient. Most patients with ADHF have evidence of volume

Table 12.1. Recommendations for Hospitalizing Patients Presenting With ADHF

Recommendation	Clinical Circumstances
(a) Hospitalization Recommended	Evidence of severely decompensated HF, including: Hypotension Worsening renal function Altered mentation Dyspnea at rest Typically reflected by resting tachypnea Less commonly reflected by oxygen saturation <90% Hemodynamically significant arrhythmia Including new onset of rapid atrial fibrillation Acute coronary syndromes
(b) Hospitalization Should Be Considered	Worsened congestion Even without dyspnea Signs and symptoms of pulmonary or systemic congestion Even in the absence of weight gain Major electrolyte disturbance Associated comorbid conditions Pneumonia Pulmonary embolus Diabetic ketoacidosis Symptoms suggestive of transient ischemic accident or stroke Repeated ICD firings Previously undiagnosed HF with signs and symptoms of systemic or pulmonary congestion

overload manifested by signs and symptoms of either pulmonary or systemic congestion (Table 12.2).[2] Many patients with signs and symptoms of volume overload will present with weight gain, although in one recent study more than half of patients admitted with acute decompensated HF had less than a two pound weight gain.[33] However, some will show no weight gain due to concomitant loss of lean body mass.

Alternatively, those patients with ADHF without obvious high-risk features may benefit from further treatment and risk-stratification in an observation unit (OU).[34] OU management has been suggested to be a safe and cost-effective alternative to hospitalization in specific subsets of patients. The majority of patients are discharged within 24 hours of admission and subsequent adverse event rates are similar to those in hospitalized subjects.[35,36]

Treatment

Recommendation

12.3 It is recommended that patients admitted with ADHF be treated to achieve the goals listed in Table 12.3. (Strength of Evidence = C)

Table 12.2. Signs and Symptoms of Congestion in HF

	Pulmonary	Systemic
Symptoms	Dyspnea	Edema
	Orthopnea	Abdominal (or hepatic) swelling and pain
	PND	Anorexia
		Early satiety
Signs	Rales	Edema
	Wheezing	Elevated JVP
	Pleural effusion and tenderness	Hepatic enlargement
	Hypoxemia	Ascites
	Third heart sound (left-sided)*	Third heart sound (right-sided)*
	Worsening mitral regurgitation	Worsening tricuspid regurgitation
		Hepatojugular reflux

*May occur without congestion.

Background

Although improving signs and symptoms are the principal immediate goals, successful inpatient therapy for worsening HF involves a comprehensive care plan. Treatment to relieve symptoms should be applied in a way that limits side effects and reduces the risk of cardiac and renal injury. Precipitating factors must be identified and chronic oral therapy optimized during the patient's hospitalization. Patients who could potentially benefit from revascularization should be identified. Education must be provided concerning dietary sodium restriction, self-assessment of volume status and principal cardiac medications. Optimizing inpatient care is critical to achieve symptom relief and low readmission rates within an acceptable period of hospitalization.

Symptom Relief. Symptoms in patients hospitalized for HF typically arise from 2 distinct causes: pulmonary or systemic congestion and poor end-organ function from inadequate cardiac output. Data from several studies demonstrate that volume expansion and congestion are far more common than symptoms arising from low cardiac output.[37] Dyspnea often improves significantly within the first few hours from diuretic and vasodilator therapy even though volume loss may not be substantial. Several additional days of hospitalization are often necessary to return the patient to a volume status that makes discharge acceptable.

Table 12.3. Treatment Goals for Patients Admitted for ADHF

Improve symptoms, especially congestion and low-output symptoms
Restore normal oxygenation
Optimize volume status
Identify etiology (see Table 4.6)
Identify and address precipitating factors
Optimize chronic oral therapy
Minimize side effects
Identify patients who might benefit from revascularization
Identify patients who might benefit from device therapy
Identify risk of thromboembolism and need for anticoagulant therapy
Educate patients concerning medications and self management of HF
Consider and, where possible, initiate a disease management program

Adverse Effects of Therapy. High-dose diuretic therapy is a marker for increased mortality during hospitalization for HF, as it is in chronic HF.[38,39] Whether this is a direct adverse effect of diuretics or a reflection of the severity of the HF is unclear. However, complications of diuretic therapy that could result in poor outcomes include electrolyte disturbance, hypotension, volume depletion, and worsening renal function. Treatments that effectively relieve symptoms in patients with ADHF, such as diuretics, morphine, vasodilators, and inodilators, can be associated with significant short- and even long-term adverse effects on renal function.

Troponin release has been documented during hospitalization for ADHF.[40] These findings suggest that myocyte loss from necrosis and apoptosis may be accelerated in patients admitted with ADHF. Mechanisms potentially accounting for cell death are still being determined but may include neurohormonal activation and pharmacologic therapy. Medications that increase myocardial oxygen demand have the potential to induce ischemia and may damage hibernating but viable myocardium, especially in patients with ischemic heart disease. Experimental data indicate that dobutamine can cause necrosis in hibernating myocardium.[41] One outcome study comparing dobutamine to levosimendan suggested greater risk in patients randomized to dobutamine.[42]

Precipitating Factors. Many episodes of worsening HF requiring hospitalization are triggered by comorbid conditions and may not be due to progressive cardiac dysfunction. Poor medication adherence, inability to maintain a restricted sodium diet, or unwillingness to follow the care plan may be the primary cause of many admissions. Not surprisingly, these factors predispose to high rates of readmission following hospital discharge.

Optimization of Oral Pharmacologic Therapy. Hospitalization for ADHF presents an excellent opportunity to restructure the patient's chronic oral medication regimen. The inpatient period is especially useful in adjusting oral therapies in patients with low blood pressure, reduced heart rate and impaired renal function, circumstances which typically make dose adjustment problematic on an outpatient basis. The need for potassium and magnesium supplementation can also be addressed.

Device Therapy. Evaluate the patient for implantable cardioverter defibrillator (ICD) or biventricular pacing therapy (see Section 9).

Education. Hospitalization provides the opportunity to enhance patients' understanding of their HF. Although retention of knowledge imparted during an admission may be limited, introduction of key concepts, including the seriousness of HF, important aspects of therapy, and monitoring volume status, sets the stage for additional education in the follow-up period. See Section 8 for additional information on patient education.

Disease Management. Referral to a disease management program for HF can be facilitated by resources in the hospital and is often a key to reducing the risk of readmission. Patients with frequent hospitalization are readily identifiable as candidates for this approach. See Section 8 of this guideline for a full discussion of disease management approaches in HF.

Recommendation

12.4 Patients admitted with ADHF should be carefully monitored. It is recommended that the items listed in Table 12.4 be assessed at the stated frequencies. (Strength of Evidence = C)

Background

The value of specific clinical assessments to monitor the response of patients admitted with ADHF has not been evaluated in controlled studies. However, there is sufficient consensus of expert opinion to support the utility of serial evaluation of specific data obtained from the history, physical examination, and laboratory findings during hospitalization.

Tracking Volume Status. Evidence that congestion is resolving should be carefully documented during hospitalization by monitoring reduction in symptoms (orthopnea, dyspnea, paroxysmal nocturnal dyspnea [PND], abdominal bloating, and edema) and signs (jugular venous pressure [JVP], rales, peripheral edema, ascites) of volume overload. Daily weights and determination of intake and output are not always accurate indicators of volume status, but still are critical in this assessment, as long as they are correlated with changes in symptoms and physical signs of fluid overload.

Blood Pressure. Blood pressure may decline significantly during hospitalization due to multiple factors including diuretic and vasodilator therapy, bed rest, and a more limited sodium intake. Although declines in blood pressure are typically well tolerated, symptomatic hypotension is an important adverse event in patients admitted with decompensated HF. Excessive or overly rapid diuresis (or overly rapid fluid removal with ultrafiltration), or excessive vasodilator therapy, even when fluid overload is still present, may produce symptomatic hypotension. Documentation of orthostatic blood pressure change on admission and after therapy may help reduce the likelihood of this side effect.

Laboratory Assessment. Serial determinations of electrolytes (especially sodium, potassium, and magnesium) and renal function (blood urea nitrogen [BUN] and serum creatinine) are necessary during diuresis. Patients may become hypokalemic and require supplemental potassium.

Table 12.4. Monitoring Recommendations for Patients Hospitalized With ADHF

Frequency	Value	Specifics
At least daily	Weight	Determine after voiding in the morning Account for possible increased food intake due to improved appetite
At least daily	Fluid intake and output	
More than daily	Vital signs	Orthostatic blood pressure if indicated Oxygen saturation daily until stable
At least daily	Signs	Edema Ascites Pulmonary rales Hepatomegaly Increased JVP Hepatojugular reflux Liver tenderness
At least daily	Symptoms	Orthopnea PND or cough Nocturnal cough Dyspnea Fatigue, lightheadedness
At least daily	Electrolytes	Potassium Sodium
At least daily	Renal function	BUN Serum creatinine*

*See background section for additional recommendations on laboratory evaluations.

Measurement of serum potassium and renal function should be performed more frequently in patients experiencing substantial diuresis (more than 2 L/day) or in patients with abnormalities in serum potassium concentration or renal function before the initiation of diuretic therapy.

Deterioration of renal function during diuresis is a poor prognostic sign and may occur even before achieving euvolemic status. Studies indicate that increasing serum creatinine is associated with an increase in morbidity and mortality in patients with ADHF.[28,29,31,32,38–45] A major dilemma occurs when creatinine rises in the face of continued signs and symptoms of congestion. Few data are available to guide clinicians to the best response to a decline in renal function in this setting. Most physicians continue diuresis as long as the increase in creatinine is modest, since failure to relieve ongoing congestion often leaves the patient symptomatic and at risk for a poor outcome. If increasing creatinine is thought to reflect intravascular volume depletion, either relative or absolute, then reduction or temporary discontinuation of diuretic or vasodilator therapy should be considered, with a reduction in the rate of diuresis to prevent a rapid depletion of intravascular volume. Adjunctive use of inotropic therapy should be considered. If substantial fluid excess persists and diuresis cannot be achieved without an unacceptable degree of azotemia, then dialysis should be considered.

The prognostic significance of worsening renal function in the setting of drug therapy is more difficult to determine. Outpatient initiation of ACE inhibitor therapy commonly increases serum creatinine, especially in severe HF. In chronic HF, modest increases have been associated with long-term reductions in mortality and hospital admissions.[46,47] Routine and frequent laboratory tests recommended in ADHF are shown in Table 12.5.

Electrolytes, BUN, creatinine. and troponin have been discussed. A complete blood count will exclude anemia. Determination of oxygen saturation will define the need for supplemental oxygen. Arterial blood gases may detect unsuspected carbon dioxide retention and suggest a comorbid pulmonary problem. Liver function tests may be elevated when there is poor hepatic perfusion or congestion or may indicate a comorbid hepatic problem. Urinalysis will exclude urinary tract infections and will help exclude acute tubular necrosis if there has been a hypotensive episode and the creatinine is rising.

Fluid Overload

Recommendation

12.5 It is recommended that patients admitted with ADHF and evidence of fluid overload be treated initially with loop diuretics - usually given intravenously rather than orally. (Strength of Evidence = B)

Ultrafiltration may be considered in lieu of diuretics. (Strength of Evidence = B)

Background

Diuretic Therapy for Decompensated HF. Although their safety and efficacy have not been established in randomized, controlled trials, extensive observational experience has demonstrated that loop diuretics, generally alone but at times in combination with non-loop diuretics, effectively relieve congestive symptoms in patients admitted with volume overload. These agents remain first line therapy for the management of congested patients with ADHF (see Section 7 Tables 7.2 and 7.3).

Observational experience also suggests that loop diuretics should be administered intravenously for best effect in the setting of worsening HF. The bioavailability of oral furosemide is highly variable from patient to patient and even from day to day in the same patient and may be considerably lower in patients with decompensated HF. Furosemide, a commonly used loop diuretic, has a short duration

Table 12.5. Laboratory Evaluation for Patients With ADHF

Routinely	Electrolytes BUN and creatinine Blood glucose Troponin Complete blood count INR if using warfarin
Frequently	BNP or NT-proBNP Liver function tests Urinalysis
Occasionally	Arterial blood gases

of action, with a peak effect at 1 to 2 hours, which resolves approximately 6 hours after dosing. Administration 2 or more times a day may be necessary and is often the best approach when these agents are initially ineffective. Increasing the dose also improves response to diuretics if the current dose is insufficient to achieve maximal delivery of drug to the tubules. Alternatively, a continuous infusion of loop diuretic may help to maintain constant drug levels at target sites in the renal tubules.

Intravenous loop diuretics can produce significant acute reductions in left and right ventricular filling pressures as rapidly as 15 minutes after administration. This helps explain why some patients experience improvement in symptoms prior to the onset of the diuretic effect of these drugs.[48] In contrast, administration of intravenous furosemide has been associated with neurohormonal activation, which may result in worsening of hemodynamics secondary to systemic vasoconstriction in the early stages of therapy.[49] However, as sodium excretion increases and diuresis ensues, volume loss leads to a reduction in cardiac filling pressures and improvement in symptoms.[49]

Ultrafiltration. Mechanical methods of fluid removal are being actively investigated as potential alternatives to pharmacologic diuresis.[50] Small uncontrolled studies have long suggested the utility of this approach using not only traditional dialysis but hemofiltration methods.[51] Initial studies supporting the use of a venovenous system, or ultrafiltration, were small and had limited outcomes.[52,53] But they did provide evidence supporting ultrafiltration as an option that may be considered for the reduction of fluid overload in acute decompensated HF. In addition, a single session of ultrafiltration was shown to reduce neurohormones and increase subsequent diuretic responsiveness.

The most extensive study of 200 patients hospitalized with HF and hypervolemia showed no effect on dyspnea at 48 hours, but did show a significant reduction in weight compared to bolus or continuous diuretics at 48 hours and an improvement in rehospitalization rates at 90 days.[54] Despite its apparent effectiveness, cost, need for venous access, and nursing support are concerns, and more study is necessary.

Recommendations

12.6 It is recommended that diuretics be administered at doses needed to produce a rate of diuresis sufficient to achieve optimal volume status with relief of signs and symptoms of congestion (edema, elevated JVP, dyspnea), without inducing an excessively rapid reduction in 1) intravascular volume, which may result in symptomatic hypotension and/or worsening renal function, or 2) serum electrolytes, which may precipitate arrhythmias or muscle cramps. (Strength of Evidence = C)

12.7 Careful repeated assessment of signs and symptoms of congestion and changes in body weight is recommended, because clinical experience suggests it is difficult to determine that congestion has been adequately treated in many patients. (Strength of Evidence = C)

12.8 Monitoring of daily weights, intake, and output is recommended to assess clinical efficacy of diuretic therapy. Routine use of a Foley catheter is not recommended for monitoring volume status. However, placement of a catheter is recommended when close monitoring of urine output is needed or if a bladder outlet obstruction is suspected of contributing to worsening renal function. (Strength of Evidence = C)

Background

Relief of congestion is a self-evident goal of diuretic therapy in congested patients admitted with worsening HF. Achieving this result, while avoiding hypotension and worsening renal function, often requires close observation and careful titration of these agents. Excessively rapid diuresis may result in symptomatic declines in blood pressure and reduced renal function, even while some degree of congestion persists.

Clinical experience suggests it may be difficult to identify persistent congestion. In contrast, even modest relief of congestion may be associated with substantial improvement in dyspnea and sense of well being in many patients despite ongoing volume overload, which may result in premature discharge. The care of patients admitted with worsening HF requires careful physical and symptom assessment and monitoring of vital signs, body weight, and laboratory results to optimize fluid status. Reduction in body weight during hospitalization should be anticipated in patients presenting with significant congestion. Careful history will often document a clear weight gain and suggest a target weight that may be desirable to achieve before discharge. However, accurate determinations of body weight and, even more so, intake and output are not easy to achieve, even in the hospital environment. These measurements should be correlated with other evidence of resolving congestion to achieve the best assessment of an adequate therapeutic response.

Recommendation

12.9 Careful observation for development of a variety of side effects, including renal dysfunction, electrolyte abnormalities, symptomatic hypotension, and gout is recommended in patients treated with diuretics, especially when used at high doses and in combination. Patients should undergo routine laboratory studies and clinical examination as dictated by their clinical response. (Strength of Evidence = C)

It is recommended that serum potassium and magnesium levels be monitored at least daily and maintained in the normal range. More frequent monitoring may be necessary when diuresis is rapid. (Strength of Evidence = C)

Overly rapid diuresis may be associated with severe muscle cramps. If indicated, treatment with potassium replacement is recommended. (Strength of Evidence = C)

Background

Overview of the Adverse Effects of Diuretics. Despite beneficial effects in acute HF, diuretics may be associated with a variety of adverse effects that often require alterations in their use or the use of concomitant medications.[55] Patients treated with diuretics should be monitored carefully for excessive urine output, development of hypotension, rise in serum BUN and creatinine levels and reductions in serum potassium, and magnesium levels. Serial determinations of creatinine and BUN are particularly important when these side effects are present or anticipated. Diuretic therapy must be highly individualized based on the degree of fluid overload present and the degree of volume loss produced to minimize these side effects.

Hypokalemia. Potassium must be monitored closely, especially during the period when diuresis is most pronounced, with supplementation given as needed. Patients with reduced serum potassium need immediate replacement before diuretic therapy for worsening HF. Aldosterone antagonists may be used cautiously in the setting of marked potassium wasting.

Hypotension. In patients with reduced LVEF and ventricular dilation, the effect of loop diuretics on cardiac output and blood pressure often seems counterintuitive. Despite decreasing filling pressures, loop diuretics usually do not produce clinically significant reductions in cardiac output or blood pressure in patients with worsening HF and LV systolic dysfunction. In patients with ventricular dilation and volume overload, total stroke volume is relatively independent of filling pressures.[56] Diuretic-induced reductions in left and right heart filling pressures are frequently accompanied by augmented forward stroke volume and cardiac output, related to (1) diminution in functional mitral regurgitation; (2) diminution in functional tricuspid regurgitation; and (3) reduction in right ventricular volume, associated with relief of ventricular-interdependent LV compression and improved effective LV distensibility.

In contrast, some patients do experience symptomatic hypotension with decreasing cardiac output and blood pressure during therapy. Intravascular volume must be maintained by reequilibration as interstitial fluid moves into the vascular bed to maintain blood pressure even as diuresis proceeds. The time course of this phenomenon varies among patients and, especially during periods of brisk diuresis, may lag behind the decline in intravascular volume, resulting in hypotension despite persistent total body fluid overload.

Diuresis accompanied by a reduction in filling pressure may make patients more sensitive to the hypotensive effects of drugs with vasodilator properties. Diuretics may significantly enhance the hypotensive effects of ACE inhibitors, even when volume overload is still present. Patients with HF with preserved LVEF or restrictive, hypertrophic, or infiltrative cardiomyopathies may be more sensitive to diuresis and may decrease their blood pressure during diuretic therapy despite continued volume expansion. All patients receiving diuretic therapy need careful monitoring to prevent adverse hemodynamic effects from excessive volume loss.

Neurohormonal Activation. Older studies demonstrated that increased activity of the renin-angiotensin and sympathetic nervous systems may occur with intravenous diuretics, and result in secondary increases in systemic vascular resistance.[57] It has been hypothesized that this acute vasoconstrictor response may play a role in the development of worsening renal function during treatment of ADHF. However, more recent studies in patients with ADHF have shown a reduction in plasma neurohormones, including norepinephrine, endothelin-1, and BNP, with parenteral diuretic and vasodilator therapy,[58] as well as following ultrafiltration.[54,59] Furthermore, the reduction in neurohormones appears to correlate with urine output and sodium excretion.[60] Whether changes in circulating neurohormones have beneficial or adverse long-term effects in patients with ADHF or alter the responsiveness to diuretic therapy requires further study.

Other Side Effects. Diuretic agents may increase the incidence of digitalis toxicity, either by decreasing glomerular filtration rate or by inducing hypokalemia and hypomagnesemia. Electrolyte disturbances induced by diuretics may result in arrhythmia. Hyponatremia may occur as a result of diuretic therapy, in part because of increases in circulating vasopressin, which can further reduce renal clearance of free water, plus an increase in free water intake in turn impeding restoration of euvolemia.[61,62] Diuretic therapy can also precipitate exacerbations of gout and at high doses cause reversible hearing loss.

Recommendation

12.10 Careful observation for the development of renal dysfunction is recommended in patients treated with diuretics. Patients with moderate to severe renal dysfunction and evidence of fluid retention should continue to be treated with diuretics. In the presence of severe fluid overload, renal dysfunction may improve with diuresis. (Strength of Evidence = C)

Background

Diuretic therapy may further worsen renal function in patients with baseline renal insufficiency. Loop diuretics may produce intrarenal regulatory changes, related in part to neurohormonal activation, which can compromise glomerular filtration rate. Excessive diuresis or overly rapid diuresis may lower preload so that systemic blood pressure is

compromised, especially in patients with marked HF with preserved LVEF and significant LV hypertrophy or restrictive physiology.

Despite these physiologic disadvantages, the net effect of diuretic therapy in individual patients with ADHF is difficult to predict. In some patients with reduced renal function at baseline, decongestion may improve serum creatinine and BUN, even as intravascular volume and filling pressures decline. Improved renal blood flow in response to relief of abdominal fluid overload is postulated as one physiologic mediator of this beneficial effect. Reduction of central venous pressure is another potential mechanism contributing to increases in glomerular filtration rate.

Recommendation

12.11 When congestion fails to improve in response to diuretic therapy, the following options should be considered:

- **Re-evaluating presence/absence of congestion**
- **Sodium and fluid restriction,**
- **Increasing doses of loop diuretic,**
- **Continuous infusion of a loop diuretic, or**
- **Addition of a second type of diuretic orally (metolazone or spironolactone) or intravenously (chlorothiazide).**

Another option, ultrafiltration, may be considered. (Strength of Evidence = C)

Background

Most patients admitted with worsened HF and congestion will respond adequately to loop diuretics with resolution of volume overload; however, a minority will experience some resistance to diuretic therapy. Increasing the frequency and then the dose of loop diuretic is recommended in these cases to restore volume status. Distal tubular diuretics augment the natriuretic effect of loop diuretics. These agents should be considered as adjunctive therapy in patients with diuretic resistance who do not respond to more frequent administration or escalating doses of loop diuretics. However, these agents can exacerbate adverse effects of loop diuretics, such as hyponatremia and hypokalemia.

Continuous infusion of a loop diuretic may produce higher and more sustained concentrations of furosemide within the renal tubule than repeated bolus injection. Continuous infusion may be associated with less prerenal azotemia and fewer other side effects compared with bolus administration, possibly because this method avoids the high peak concentrations associated with bolus dosing. [63]

Recommendation

12.12 A low sodium diet (2 g daily) is recommended for most hospitalized patients. (Strength of Evidence = C)

In patients with recurrent or refractory volume overload, stricter sodium restriction may be considered. (Strength of Evidence = C)

Background

Restricting fluid intake to 2 L/day is usually adequate for most hospitalized patients. Dietary sodium restriction is important, even short-term in the hospital setting, to help restore euvolemia. The level of sodium restriction prescribed during hospitalization may be greater than typically feasible in the outpatient setting. Education regarding sodium and fluid restriction may be initiated during an admission.[64]

Recommendation

12.13 Fluid restriction (<2 L/day) is recommended in patients with moderate hyponatremia (serum sodium <130 mEq/L) and should be considered to assist in treatment of fluid overload in other patients. (Strength of Evidence = C)

In patients with severe (serum sodium <125 mEq/L) or worsening hyponatremia, stricter fluid restriction may be considered. (Strength of Evidence = C)

Background

Severe hyponatremia is not a common manifestation of ADHF, but is an ominous sign. However, recent results suggest that even reductions in serum sodium traditionally considered mild (<137 mEq/L) are associated with prolonged hospitalization and increased in-hospital mortality.[65] Patients whose reduction in serum sodium is related to volume depletion as a result of diuretic therapy or environmental conditions will respond to administration of sodium and water. However, the great majority of hyponatremia in HF patients occurs in the setting of volume overload and cannot be corrected by the administration of sodium, which will only compound volume expansion.

Fluid restriction may produce some improvement in serum sodium concentration and may be transiently effective in mild hyponatremia. Fluid restriction can be difficult to maintain, because thirst is a common symptom in patients with HF. Patients may feel a certain amount of fluid ingestion is necessary for good health and that restriction will be harmful. Education concerning the benefits and lack of adverse effect of fluid restriction may help promote adherence. In patients with HF, hyponatremia is associated with a higher risk of clinical deterioration, including renal and hepatic dysfunction, longer hospital stays and high rehospitalization and mortality rates.[66–69] The degree of hyponatremia is inversely associated with mortality.[69] Hyponatremia in patients with HF is due to an inability to excrete free water, primarily due to neurohormonal activation. Increases in norepinephrine and angiotensin II result in decreased delivery of sodium to the distal tubule by causing decreased renal

perfusion, while arginine vasopressin increases water absorption from the distal tubule. In addition, angiotensin II directly promotes thirst. Thus serum sodium is a marker for poor cardiac output and neurohormonal activation.

Recently it has been suggested that hyponatremia may be associated with more neurocognitive symptoms than previously recognized. In a case-control study of 122 patients (none with HF) with hyponatremia (serum sodium 126 ±5 mEq/L), falls and attention deficits were far more common in the hyponatremic patients.[70] Treatment of hypervolemic hyponatremia with a V2-selective vasopressin antagonist (tolvaptan) was associated with a significant improvement in The Mental Component of the Medical Outcomes Study 12 item Short Form General Health Survey.[71]

Treatment of hyponatremia consists of water restriction and maximization of medical therapies such as ACE-inhibitors or angiotensin receptor blockers which block or decrease angiotensin II, resulting in improved renal perfusion and decreased thirst. Vasopressin antagonists have been shown to improve serum sodium in hypervolemic, hyponatremic states with either a V2-selective or a non-selective vasopressin antagonist.[71,72] Longer term therapy with a V2 selective vasopressin antagonist does not improve mortality but appears to be safe.[73,74] Currently two vasopressin antagonists are available for clinical use (conivaptan and tolvaptan) and only short-term studies are available. At present it may be reasonable to utilize a non-selective vasopressin antagonist to treat hyponatremia in patients with HF who are observed to have significant cognitive symptoms due to hyponatremia. However, the long-term safety and efficacy of this approach remains unproven. In patients with refractory hyponatremia, alternative causes (e.g., hypothyroidism, hypoaldosteronism, syndrome of inappropriate antidiuretic hormone) should be excluded.

Recommendation

12.14 Routine administration of supplemental oxygen in the presence of hypoxia is recommended. (Strength of Evidence = C)

Routine administration of supplemental oxygen in the absence of hypoxia is not recommended. (Strength of Evidence = C)

Background

Routine oxygen administration in patients with acute HF is recommended to improve oxygen delivery to vital organs, including the myocardium. While there have been no randomized trials to support this, improving systemic and myocardial hypoxemia would be expected to improve the overall clinical status of patients with acute HF.

Supplemental oxygen therapy should be individualized. The congested dyspneic patient who presents with hypoxemia requires oxygen therapy. Patients with systemic fluid overload that does not compromise oxygenation do not require oxygen therapy. Supplemental oxygen in the setting of normal oxygen saturations on room air could be problematic if the patient also has a history of obstructive lung disease. In selected patients, oxygen may decrease elevated pulmonary vascular resistance and improve right heart function. Supplemental oxygen is also recommended in patients with acute myocardial infarction (MI) complicated by HF. The role of nocturnal oxygen in patients with central sleep apnea remains unproven.

Recommendation

12.15 Use of non-invasive positive pressure ventilation may be considered for severely dyspneic patients with clinical evidence of pulmonary edema. (Strength of Evidence = A)

Background

Previous small trials investigating the use of noninvasive ventilation (NIV) in emergency department patients with acute HF suggested it improved symptoms, decreased the need for subsequent intubation and reduced mortality.[75–77] There were some concerns from one of the early trials that bi-level positive pressure ventilation may have led to an increase in the number of patients with myocardial infraction.[78] However, a subsequent study did not encounter this association, and a review of data from the original trial suggests that a disproportionate number of patients with evolving MI may have been enrolled in the interventional arm.[79,80] Several subsequent meta-analyses based on these smaller NIV trials also suggested that both intubation rates and mortality were reduced with NIV.[81–83] However, results from a recent large randomized trial in the United Kingdom suggest while NIV improved patient's dyspnea and metabolic abnormalities, it did not significantly change mortality and intubation rates when compared to standard oxygen therapy.[84] Further, the authors found no significant differences in efficacy between continuous positive pressure ventilation and bi-level positive pressure ventilation. While this study has rather robust results and randomized over 1100 patients, it is worth noting that concomitant therapy was not standardized, opioids were used in over 50% of patients, and over 15% of patients on standard therapy crossed over to NIV. Further, the primary endpoint was measured at 7 days, a time far removed from the time frame of use of NIV. Despite those limitations, the preponderance of evidence suggests NIV is a useful temporizing measure that improves dyspnea but likely has no impact on intubation rates or mortality.

Prevention of Deep Venous Thrombosis and Pulmonary Embolism

Recommendation

12.16 Venous thromboembolism prophylaxis with low dose unfractionated heparin (UFH), low molecular weight heparin (LMWH), or fondaparinux

to prevent proximal deep venous thrombosis (DVT) and pulmonary embolism (PE) is recommended for patients who are admitted to the hospital with ADHF and who are not already anticoagulated and have no contraindication to anticoagulation. (Strength of Evidence = B)

Venous thromboembolism prophylaxis with a mechanical device (intermittent pneumatic compression devices or graded compression stockings) to prevent proximal DVT and PE should be considered for patients who are admitted to the hospital with ADHF and who are not already anticoagulated and who have a contraindication to anticoagulation. (Strength of Evidence = C)

Background

Prevention of DVT and PE remain important management issues in hospitalized patients. Ten percent of hospital deaths are considered to be due to PE and the prevention of DVT and PE is considered the most valuable of 79 preventative initiatives outlined by the Agency for Healthcare Research and Quality.[85,86] NYHA Class III and IV HF is a major risk factor for DVT and acute hospitalization increases the risk of DVT several-fold.[87,88] One million patients per year are admitted for acutely decompensated HF in both the US and Europe.[89] With an in-hospital mortality for decompensated HF of approximately 4%, as many as 4000 patients deaths due to PE are potentially preventable yearly in both the US and Europe.[90,91] Although no large randomized trial of DVT prophylaxis has been conducted solely in an acute decompensated HF population, several randomized trials conducted in hospitalized patients that have included a large percentage of patients admitted for decompensated HF.[92–98] Prophylaxis with low dose UFH, LMWH, and fondaparinux have been shown to decrease the incidence of asymptomatic DVT and in some cases symptomatic DVT.[92–98] Only one trial has independently demonstrated a benefit of anticoagulation prophylaxis on PE and that trial was conducted in patients with infectious diseases.[99] Two meta-analyses have reported a significant benefit of either low dose UFH or LMWH on DVT and PE without an effect on mortality and with a non-significant increase in the risk of major bleeding.[100,101] All but two of the studies in these meta-analyses included patients admitted with decompensated HF. The American College of Chest Physicians has given DVT prophylaxis with UFH or LMWH a 1A recommendation for acutely hospitalized patients with a high risk for DVT and NYHA Class III or IV HF is considered a high-risk category.[85] Although no single trial has been conducted in only hospitalized patients with HF, a subgroup analyses of two large randomized trials demonstrates a significant benefit of LMWH on DVT in HF patients.[102,103] No large study compares UFH to LMWH or fondaparinux, but a meta-analysis of all studies suggests a trend in favor of LMWH compared to low dose UFH for both reduction of DVT and PE with a trend for less bleeding.[104]

LMWH are renally excreted and should not be used in patients with a creatinine clearance <30 mL/min. LMWH should also be avoided in patients with HF who have undergone a recent surgical procedure, such as an ICD implantation.

Mechanical means of DVT prophylaxis, such as intermittent pneumatic compression devices or graded compression stockings, have not been subjected to randomized trials in medical patients and are reserved for patients with contraindications to anticoagulation.[85] Graded compression stockings may be preferable if intermittent pneumatic compression devices limit patient mobility.[104]

At the time of admission, screening for venous thromboembolism is indicated when patients present with unilateral or asymmetric lower extremity edema, chest pain, or presyncope. Worsening right HF and pulmonary hypertension may also be signs of chronic pulmonary emboli.

IV Vasodilators

Recommendation

12.17 In the absence of symptomatic hypotension, intravenous nitroglycerin, nitroprusside or nesiritide may be considered as an addition to diuretic therapy for rapid improvement of congestive symptoms in patients admitted with ADHF. (Strength of Evidence = B)

Frequent blood pressure monitoring is recommended with these agents. (Strength of Evidence = B)

These agents should be decreased in dosage or discontinued if symptomatic hypotension or worsening renal function develops. (Strength of Evidence = B).

Reintroduction in increasing doses may be considered once symptomatic hypotension is resolved. (Strength of Evidence = C)

Background

Nitroglycerin. Intravenous nitroglycerin acutely reduces LV filling pressure, primarily through its venodilator effects, which reduce pulmonary congestion.[106] At higher doses the drug may lower systemic afterload and increase stroke volume and cardiac output, but the extent of these effects is variable. Intravenous nitroglycerin may improve coronary blood flow, making it potentially more effective in patients with ADHF from acute ischemia or MI. Nitroglycerin therapy results in neurohormonal activation; whether this has a detrimental effect in acute HF is uncertain.[105,106]

Data demonstrating favorable hemodynamic effects of intravenous nitroglycerin in HF are derived primarily from small, uncontrolled studies of patients who were not usually hospitalized for acute decompensation.[107] These

studies demonstrate beneficial hemodynamic effects, but also document a relative resistance to nitroglycerin and significant tachyphylaxis to the vascular actions of this drug, changes that can occur within hours at high doses. The strategy of a nitrate-free interval, which may be an option to reduce tolerance during chronic therapy, could result in adverse hemodynamic effects that would be unacceptable in patients with acute HF.

Approximately 20% of patients with HF are resistant to the hemodynamic effects of any dose of nitroglycerin.[108,109] Patients who do not have hemodynamic benefit at doses of intravenous nitroglycerin in the range of 200 μg/kg can be considered non-responders for whom additional dosing is unwarranted.

The adverse effects of nitroglycerin therapy include headache, abdominal discontent, and symptomatic hypotension.[110] Hypotension is more likely when preload is low, which may occur as filling pressures decline in response to diuretic therapy. Symptomatic hypotension and headache respond to reduction in dose, but may require discontinuation of therapy.

Nitroprusside. This potent vasodilator has balanced effects on the venous and arteriolar tone. PCWP is reduced almost immediately, and there usually is a robust increase in cardiac output. The drug is used primarily in conjunction with hemodynamic monitoring. It can be easily titrated to an appropriate dose while maintaining a systolic blood pressure >90 mm Hg or mean arterial pressure >65 mm Hg. The dose range is between 5 and 300 mcg/minute. Thiocyanate toxicity may occur gradually in patients with renal dysfunction, but is rare when nitroprusside is used by an experienced care team.[111]

Nesiritide. A number of cardiovascular, renal, and neurohormonal effects of BNP have been identified.[112,113] Nesiritide, a peptide identical to human BNP, represents the form of BNP available for clinical use. Extensively evaluated in patients with HF from almost exclusively LV systolic dysfunction, nesiritide administration produces dose-dependent reductions in filling pressure, systemic and pulmonary vascular resistance, and an increase in cardiac output.[114–117] At the currently recommended dose (0.01 μg/kg), nesiritide significantly reduces LV filling pressure but has variable effects on cardiac output.[110] A reduction in circulating aldosterone levels has been observed.[118]

Studies of nesiritide in patients with HF from LV systolic dysfunction show no consistent effect on glomerular filtration rate and renal blood flow. Some studies have demonstrated enhanced urinary output and increased sodium excretion, while others have not.[118,119] A number of explanations have been proposed for these variable effects, including the dose of nesiritide studied, degree of concomitant diuretic therapy, and hemodynamic effects, which may include a reduction in blood pressure or an augmentation of cardiac output.

The VMAC Trial. The Vasodilator in the Management of Acute Heart Failure (VMAC) study was a complex multicenter, randomized, double-blinded controlled trial of nesiritide, nitroglycerin, and standard therapy in 489 patients hospitalized for worsening HF.[110] The study used a dose of nesiritide (bolus of 2 μg/kg followed by an infusion of 0.01 μg/kg/min) .The primary endpoints of the VMAC trial were change in PCWP from baseline (catheterized stratum only) and change in dyspnea score from baseline. The primary study comparison of these endpoints was between nesiritide on top of standard therapy versus standard therapy alone at 3 hours.

Trial results showed that the combination of nesiritide plus standard therapy significantly decreased PCWP ($P < .001$) and dyspnea score ($P = .03$) at 3 hours compared with standard therapy alone. Nesiritide did not improve dyspnea compared to nitroglycerin, but did lower the PCWP more than nitroglycerin ($P = .03$). However, the nitroglycerin doses used in VMAC were relatively small and may account for the observed differences in PCWP.

Adverse Effects. The potential side effects of nesiritide include hypotension, headache, and worsening renal function. The risk of hypotension appears to be dose dependent and was less frequent in the VMAC study than in earlier trials that used higher maintenance doses. The incidence of symptomatic hypotension in the VMAC trial was similar in patients treated with nitroglycerin versus nesiritide. Because of the longer effective half-life of nesiritide, hypotension may last longer with nesiritide than with nitroglycerin. Headache is not a common or severe side effect of nesiritide.

Worsening Renal Function. Worsening of renal function has been observed in clinical trials with nesiritide. The mechanisms for this adverse effect on renal function are unknown but physiologic considerations suggest interaction with diuretic therapy, reductions in blood pressure and inhibition of the renin angiotensin aldosterone system may play a role. Only limited data are available from clinical trials to assess the frequency and severity of this adverse effect. Analysis of available data from the VMAC study and other nesiritide trials demonstrated that nesiritide plus standard therapy was more likely than standard therapy alone to be associated with a rise in creatinine of >0.5 mg/dL during the study period.[120] This analysis was retrospective and used data from studies that were not prospectively designed to assess serial changes in renal function. The cut point of serum creatinine used to indicate worsening renal function was dictated by the data available to the investigators and has been employed in other studies. Whether there is a general relationship between nesiritide and worsening renal function or whether other cut points of creatinine increase would show a similar adverse effect is unknown. Although most of the clinical trials of nesiritide were not designed to monitor effects on renal function for a 30-day period, analysis of any additional data available is needed.

The dose of nesiritide may be a significant factor related to the risk of worsening renal function. In the VMAC study worsening renal function, as defined by the 0.5 mg/dL endpoint, occurred in 21% of patients randomized to standard therapy plus nitroglycerin versus 27% in the patients randomized to nesiritide.[120]

Whether the worsening renal function induced by nesiritide is associated with adverse outcomes in patients with ADHF is uncertain. Additional mechanistic studies are needed to better understand the effects of nesiritide on renal function, both regarding glomerular filtration rate and urinary sodium excretion, and how this may vary with diuretic use and volume status in patients with ADHF.

Outcome Data. The current guideline has specified that nesiritide may be considered for symptom relief in patients with symptomatic congestion. A recent meta-analysis has suggested that use of nesiritide in patients with ADHF is associated with increased mortality.[121] However, the data overall do not provide convincing evidence of an adverse effect. Similar evaluations for intravenous nitroglycerin and nitroprusside in patients with ADHF are not available. Well designed and adequately powered prospective studies are warranted to determine the effect of this drug on outcomes in patients with ADHF.

Morphine

Morphine has been used as adjunctive therapy in acute HF for several decades. Though its beneficial mechanism of action in acute HF is unclear, it is thought to produce mild venodilation and preload reduction.[122,123] Further, it may impart a beneficial effect through relief of anxiety and a diminished catecholamine response. However, prospective data supporting its use is limited. Retrospective data suggest an association between morphine use and adverse outcomes such as endotracheal intubation, intensive care unit admission and prolonged hospital length of stay.[124,125] A recent Acute Decompensated Heart Failure National Registry (ADHERE) analysis suggests the use of morphine was also associated with increased in-hospital mortality.[126] Much of this data is confounded by the possibility that those patients who were ''sicker'' received morphine. Prospective study is necessary to determine the risks and benefits of morphine use. If used at all in acute HF, it should be used with caution, especially in those patients with abnormal mental status and impaired respiratory drive.

Recommendation

12.18 Intravenous vasodilators (nitroglycerin or nitroprusside) and diuretics are recommended for rapid symptom relief in patients with acute pulmonary edema or severe hypertension. (Strength of Evidence = C)

Background

Diuretics remain an important treatment for acute pulmonary edema, although randomized controlled trial data to establish the best strategy for the use of these agents (eg, duration and dose of this therapy) are not available. Data from contemporary randomized controlled clinical trials demonstrating the benefit of vasodilator therapy plus standard therapy compared with standard therapy alone are also lacking. Support for the use of these agents comes from extensive clinical experience in patients admitted with this syndrome, which suggests benefit is common. In addition, one study has suggested that intravenous isosorbide dinitrate and low-dose diuretics might be more effective than high-dose diuretics in patients with this condition. In this trial, 110 patients were randomized to treatment with (1) repeated high-dose boluses of intravenous isosorbide dinitrate plus a single 40-mg bolus of intravenous furosemide or (2) repeated high-dose furosemide. These regimens were administered until oxygen saturation was above 96% or mean arterial blood pressure decreased by 30% or to below 90 mm Hg. Patients randomized to repeated high doses of isosorbide dinitrate and a low-dose diuretic had a significantly lower combined risk of MI, requirement for mechanical ventilation or death than those treated primarily with a more aggressive diuretic regimen.[127] Similar results were also seen in an ED-based non-randomized trial of high dose nitroglycerin in the treatment of severe decompensated HF.[128]

Recommendations

12.19 Intravenous vasodilators (nitroprusside, nitroglycerin, or nesiritide) may be considered in patients with ADHF who have persistent severe HF despite aggressive treatment with diuretics and standard oral therapies.

- **Nitroprusside (Strength of Evidence = B)**
- **Nitroglycerine, Nesiritide (Strength of Evidence = C)**

12.20 Intravenous inotropes (milrinone or dobutamine) may be considered to relieve symptoms and improve end-organ function in patients with advanced HF characterized by LV dilation, reduced LVEF, and diminished peripheral perfusion or end-organ dysfunction (low output syndrome), particularly if these patients have marginal systolic blood pressure (< 90 mm Hg), have symptomatic hypotension despite adequate filling pressure, or are unresponsive to, or intolerant of, intravenous vasodilators. (Strength of Evidence = C)

These agents may be considered in similar patients with evidence of fluid overload if they respond poorly to intravenous diuretics or manifest diminished or worsening renal function. (Strength of Evidence = C)

When adjunctive therapy is needed in other patients with ADHF, administration of vasodilators should be considered instead of intravenous inotropes (milrinone or dobutamine). (Strength of Evidence = C)

Intravenous inotropes (milrinone or dobutamine) are not recommended unless left heart filling pressures are known to be elevated or cardiac index is severely impaired based on direct measurement or clear clinical signs. (Strength of Evidence = C)

It is recommended that administration of intravenous inotropes (milrinone or dobutamine) in the setting of ADHF be accompanied by continuous or frequent blood pressure monitoring and continuous monitoring of cardiac rhythm. (Strength of Evidence = C)

If symptomatic hypotension or worsening tachyarrhythmias develop during administration of these agents, discontinuation or dose reduction should be considered. (Strength of Evidence = C)

Background

Introduction. Although they account for only a small percentage of ADHF, patients with advanced HF, which may be defined by severe LV systolic dysfunction with ventricular dilation and marked chronic clinical symptoms, represent a major therapeutic challenge.[129,130] Treatment options are limited and there is little evidence from randomized trials to guide management. Marked resting hemodynamic derangements, such as reduced cardiac output and increased PCWP, are characteristic in these patients. Available clinical studies have assessed the effect of treatment almost exclusively on hemodynamic endpoints. These studies provide convincing evidence that administration of vasodilators and inotropic agents, alone or in combination, usually results in significant short-term hemodynamic improvement in most patients. Many patients with advanced HF and ADHF will have moderate to severe vasoconstriction and substantially elevated filling pressures, a hemodynamic pattern that may improve with vasodilators alone.

Intravenous inotropes (milrinone or dobutamine) may be considered to relieve symptoms and improve end-organ function in patients with advanced HF and diminished peripheral perfusion or end-organ dysfunction (low output syndrome). Inotropic therapy is often used if these patients have marginal systolic blood pressure (<90 mm Hg), have symptomatic hypotension despite adequate filling pressure, or are unresponsive to, or intolerant of, intravenous vasodilators. Patients with advanced HF and reduced blood pressure and normal or low systemic vascular resistance often will not tolerate or derive sufficient hemodynamic benefit from vasodilator therapy. Inotropic agents may be necessary to maintain circulatory function in these patients. Even patients with advanced HF may present with ''low cardiac output'' syndrome due to volume depletion. Elevation of left heart filling pressures based on classical signs and symptoms or direct measurement should be documented prior to use of vasodilators or inotropic agents in patients with advanced HF. Vasodilators and inotropic agents may be considered in patients with advanced HF with evidence of fluid overload if they respond poorly to intravenous diuretics or manifest diminished or worsening renal function.

Administration of intravenous inotropes (milrinone or dobutamine) in the setting of ADHF and advanced HF should be accompanied by continuous or frequent blood pressure monitoring and continuous monitoring of cardiac rhythm. Discontinuation or dose reduction is often necessary if the use of vasodilators or inotropic agents is accompanied by symptomatic hypotension. Inotropic agents may promote or aggravate tachyarrhythmias and discontinuation or reduction in dose may be necessary when these side effects occur. The effects of dobutamine may wane with time (tachyphylaxis) or be negated by development of hypersensitivity myocarditis.

Data concerning the hemodynamic effects of intravenous nitroglycerin and nesiritide are reported elsewhere; this background section will focus on the use of sodium nitroprusside and inotropic agents in patients with advanced HF.

Sodium Nitroprusside. Sodium nitroprusside exerts a significant effect on both ventricular preload and afterload, resulting in both a decrease in LV filling pressures and typically an increase in LV stroke volume. After-load reduction may be of particular benefit in patients with acute HF complicated by significant mitral regurgitation, making sodium nitroprusside effective in these patients. This drug can be used to establish reversibility of pulmonary hypertension in patients being evaluated for cardiac transplantation. Sodium nitroprusside may prove useful in patients with ADHF associated with LV dysfunction and severe aortic stenosis.

Despite these favorable hemodynamic effects, sodium nitroprusside has not been widely adopted as a treatment modality for acute HF. There are a number of aspects related to the pharmacologic effects of the drug and its practical application that have limited its use in ADHF. In most centers, this drug is not administered without invasive monitoring of blood pressure and typically central hemodynamics. In the absence of HF, sodium nitroprusside has been noted to increase mortality rates when given within 48 hours of an acute MI.[70] One explanation for this adverse effect centers on the significant effects the drug may have on coronary blood flow. Coronary artery disease may limit the vasodilatory response to nitroprusside and thus create a circumstance of coronary steal with improved perfusion through normal vessels and reduced blood flow through diseased arteries. However, when pump dysfunction persists for greater than 48 hours after acute MI, nitroprusside may improve survival.[131]

Sodium nitroprusside should be initiated at a rate dose of 5-10 μg/min. Doses exceeding 400 μg/min generally do not produce added benefit and may increase the risk of thiocyanate toxicity. The drug may be titrated rapidly (up to every 5 minutes) until hemodynamic goals are reached. Caution is advised when discontinuing nitroprusside and monitoring for rebound vasoconstriction is warranted.[132]

Milrinone and Dobutamine. Milrinone, often termed an inodilator, causes, in the short term, increased myocardial contractility and decreased systemic and pulmonary vascular tone.[133] Heart rate typically is augmented to a lesser degree with milrinone than dobutamine, but both drugs may cause unwanted tachycardia. Milrinone typically produces significant vasodilation of the pulmonary arterial system, which may be important in supporting patients with marked pulmonary hypertension and poor cardiac output. Milrinone administration may demonstrate that increased pulmonary resistance is reversible,[134] an important observation in patients being considered for cardiac transplantation. Because dobutamine does not act as a direct pulmonary vasodilator, it typically has little effect on pulmonary vascular resistance. There is always concern that inotropic agents may increase myocardial oxygen consumption. In a small study of 10 patients, the use of milrinone was not associated with increased myocardial oxygen consumption from baseline.[135]

In contrast to dobutamine, the hemodynamic effects of milrinone are not mediated by stimulation of beta receptors. Thus the pharmacologic actions of milrinone do not appear to be diminished to the same extent as those of dobutamine by concomitant administration of beta blocking drugs. To avoid discontinuation of beta blockade, some clinicians use this agent for hemodynamic support of patients who are hospitalized with worsening HF while on beta blocker therapy. In patients with advanced dilated cardiomyopathy, the positive inotropic effects of dobutamine or milrinone may be highly variable and it is critical to titrate doses to desired clinical and hemodynamic effect.

Dosing. Bolus administration of milrinone definitely produces rapid hemodynamic improvement, but is associated with increased risk of symptomatic hypotension. Symptomatic hypotension occurred in more than 10% of patients in the milrinone arm of the Outcomes of a Prospective Trial of Intravenous Milrinone for Exacerbations of Chronic Heart Failure (OPTIME-CHF), even though the initial dose was 0.5 μg/kg/min without a bolus.[50] However, recent work has shown that by 2 hours, the hemodynamic improvement from this infusion rate is similar with or without a loading dose.[136] An increase of approximately 50% in cardiac index occurs during this brief period. Initial doses of 0.1 μg/kg/min and final doses of 0.2 to 0.3 μg/kg/min should be considered, as they appear to be associated with symptomatic improvement and may be better tolerated, but the recommended dose range goes up to 0.75 μg/kg/min.

Risks of Inotropic Agents. Data from at least 2 studies confirm that there is no rationale for the use of inotropic agents in the great majority of patients admitted with acute HF with congestion who are not in a low output state.[2,37] No clinical benefits and evidence of adverse effects were found from the administration of milrinone in the OPTIME-CHF study. In addition, results from an observational analysis of the patients enrolled in the ADHERE registry suggest that this class of drugs is associated with an adverse effect on mortality among patients currently hospitalized with acute HF, the great majority of whom have elevated or normal blood pressure and congestion.[65,137]

Acute HF appears to represent a period during which the myocardium is at risk of additional damage, especially in patients with advanced HF, who are more likely to be treated with inotropic support. In this setting, there is concern that inotropic agents may: (1) increase heart rate, (2) adversely affect coronary flow to ischemic segments, (3) augment myocardial oxygen consumption, and (4) produce symptom relief with less reduction in filling pressure. These factors may all contribute to loss of additional cardiomyocytes and promote progressive HF.

Consideration of the OPTIME-CHF trial may further illustrate the limitations of inotropic therapy in broad populations of patients with ADHF. This study was a randomized, controlled, double-blind trial that tested the potential benefit of inotropic agents in patients admitted with ADHF and systolic dysfunction, but without "low-output syndrome"—a population not usually considered for inotropic therapy. A total of 949 patients were randomized to a 48-hour infusion of milrinone (0.5 μg/kg/min) or placebo within 48 hours of admission. Patients were excluded if, in the opinion of the investigator, they had an absolute requirement for inotropic therapy. Also excluded were those with a history of poor rate control of atrial fibrillation, a history of ventricular arrhythmia, or myocardial ischemia in the past 3 months. The primary end point of the study was rehospitalization for a cardiovascular cause within 60 days.

OPTIME-CHF demonstrated that the median number of days patients were hospitalized for cardiovascular causes did not differ significantly between patients given milrinone and those given placebo. Milrinone therapy showed early treatment failure and was associated with a nonsignificant higher number of deaths in hospital and within 60 days. The use of milrinone resulted in significantly higher incidence of new atrial arrhythmias and of sustained systolic BP of <80 for 30 minutes, requiring intervention. The study authors concluded that milrinone therapy was not indicated for routine use as an adjunct to standard therapy in patients with an exacerbation of HF.[138]

Potential Role for Inotropic Therapy. Careful patient selection is required to achieve a favorable risk-benefit ratio for inotropic therapy. Although ongoing clinical studies strongly suggest that inotropic therapy is not effective in broad populations of patients with ADHF, there are instances in which these drugs are necessary to maintain cardiac

output and may be more effective in the short-term for this purpose than vasodilators. Inotropic drugs may be considered in the highly selected patients described in recommendation 12.20. These patients often present with hypotension and may face an increased risk of further hypotension from vasodilator agents. Clinical experience indicates that patients with ''low cardiac output'' syndrome and reduced renal function may respond to inotropic support with diuresis and improved renal function. Patients presenting with cardiogenic shock may need inotropes to maintain the minimal cardiac output necessary for survival. In these cases, inotropes can be a ''bridge'' to more definitive therapy, such as revascularization, cardiac transplantation, or mechanical circulatory support. The use of inotropic agents as palliative care in patients who are not candidates for more definitive therapy recognizes that improvement in quality of life and clinical status may be all that is possible in certain patients and may be achieved at the expense of increased mortality during therapy. However, morbidity, such as non-related infection from central venous catheters used to administer the drugs, should also be considered.

Hemodynamic Monitoring

Recommendations

12.21 The routine use of invasive hemodynamic monitoring in patients with ADHF is not recommended. (Strength of Evidence = A)

12.22 Invasive hemodynamic monitoring should be considered in a patient:

- **who is refractory to initial therapy,**
- **whose volume status and cardiac filling pressures are unclear,**
- **who has clinically significant hypotension (typically SBP < 80 mm Hg) or worsening renal function during therapy, or**
- **who is being considered for cardiac transplant and needs assessment of degree and reversibility of pulmonary hypertension, or**
- **in whom documentation of an adequate hemodynamic response to the inotropic agent is necessary when chronic outpatient infusion is being considered. (Strength of Evidence = C)**

Background

Treating symptoms and improving the hemodynamic profile of patients admitted with HF generally can be guided by skilled clinical assessment and laboratory evaluation. Direct hemodynamic monitoring by right heart catheterization has been advocated in the management of hospitalized patients with advanced HF to (1) guide therapy by permitting direct tracking of filling pressures and systemic vascular resistance until certain specific hemodynamic goals are reached and (2) assist in understanding volume status and tissue perfusion by direct determination of the extent and type of hemodynamic abnormalities present.[139]

The first concept, that treatment to a specific hemodynamic goal through the use of invasive hemodynamic monitoring may be of value in patients admitted with advanced HF, has been evaluated recently in the Evaluation Study of Congestive Heart Failure and Pulmonary Artery Catheterization Effectiveness (ESCAPE) trial.[140] Hemodynamically guided therapy did not increase the number of days alive and out of hospital over the course of 6 months compared with standard management alone.[141]

Given the neutral results of ESCAPE, it is reasonable to ask whether or not there are patients admitted with ADHF who still need invasive hemodynamic monitoring. Patients with a clear clinical need for right heart catheterization were excluded from ESCAPE. Examples would include patients with cardiogenic shock. Uncertainty concerning the hemodynamic state of individual patients following careful clinical evaluation and initial therapy remains a reasonable indication for direct determination of hemodynamics. Invasive monitoring may benefit patients who are hypotensive, fail to respond to diuretic therapy, or have worsening renal function but unknown filling pressures and cardiac output. The need for invasive hemodynamics often becomes apparent as treatment progresses.

Clinical estimation or measurement of right atrial pressure usually correlates with left-sided filling pressures both at a single time point and during changes induced by medications. However, pulmonary disease or disproportionate right HF may alter this relationship. Right heart catheterization can assess LV filling pressures as long as accurate PCWP tracings can be obtained and there is no significant stenosis of the pulmonary veins or mitral valve. Complications associated with use of intra-cardiac catheters include ventricular arrhythmias and line-related infection. Incorrect interpretation of hemodynamic data or overtreatment based on data may also lead to adverse outcomes.[142,143]

Precipitating Factors

Recommendation

12.23 It is recommended that patients admitted with ADHF undergo evaluation for the following precipitating factors: atrial fibrillation or other arrhythmias (eg, atrial flutter, other supraventricular tachycardia or ventricular tachycardia), exacerbation of hypertension, myocardial ischemia/infarction, exacerbation of pulmonary congestion, anemia, thyroid disease, significant drug interactions, and other less common factors. (Strength of Evidence = C)

Background

A number of precipitating factors (see Table 12.6) may worsen cardiac function and volume status, resulting in an episode of ADHF. Proper detection and treatment of

Table 12.6. Common and Uncommon Precipitating Factors Associated With Hospitalization for ADHF

Dietary and medication related causes
Dietary indiscretion - excessive salt or water intake
Nonadherence to medications
latrogenic volume expansion
Progressive cardiac dysfunction
Progression of underlying cardiac dysfunction
Physical, emotional, and environmental stress
Cardiac toxins: alcohol, cocaine, chemotherapy
Right ventricular pacing
Cardiac causes not primarily myocardial in origin
Cardiac arrhythmias: atrial fibrillation with a rapid ventricular response, ventricular tachycardia, marked bradycardia, and conduction abnormalities
Uncontrolled hypertension
Myocardial ischemia or infarction
Valvular disease: progressive mitral regurgitation
Non-cardiac causes
Pulmonary disease - pulmonary embolus, COPD
Anemia, from bleeding or relative lack of erythropoietin or bone marrow suppression
Systemic infection; especially pulmonary infection, urinary tract infection, viral illness
Thyroid disorders
Adverse cardiovascular effects of medications
Cardiac depressant medications
Nondihydropyridine calcium antagonists
Type la and Ic antiarrhythmic agents
Sodium retaining medications
Steroids
Nonsteroidal anti-inflammatory drugs, COX-2 inhibitors, thiazolidinediones, pregabalin

precipitating factors is an important part of the management of ADHF and a key to preventing recurrent episodes.

Process of Care and Adherence Issues. A number of factors not directly related to the circulatory pathophysiology of HF often contribute in a substantial way to hospitalization for ADHF. These precipitating factors are the target of disease management programs which are a critical factor in limiting recurrent admission for HF in many patients.

Dietary Indiscretion. Excessive sodium intake is a well recognized precipitating factor for admission for ADHF. Less well understood is the role of excessive water intake. A careful review of the patient's dietary history is a critical part of the assessment of patients admitted with ADHF.

Medication Nonadherence. Lack of access to medication for financial reasons or from access to care problems is a major cause of nonadherence which may be addressed during hospital admission.

Latrogenic Volume Overload. ADHF may be precipitated by inappropriate administration of fluid related to surgical or other procedures. Volume status may be difficult to assess in certain clinical conditions (eg, pulmonary infection) and inaccurate assessment of volume status may yield to unwarranted volume replacement. Patients with chronic HF and symptomatic hypotension do not require fluid resuscitation, and those with mild orthostatic hypotension may improve with liberalization of oral fluid intake.

Progressive Cardiac Dysfunction. Progression of underlying cardiac dysfunction with ventricular remodeling is an important cause of ADHF and if present will necessitate changes in chronic therapy. Progressive cardiac dysfunction is not always a consequence of worsening underlying disease, but may reflect adverse concomitant problems, such as pneumonia, uncontrolled diabetes, alcohol withdrawal, or cocaine use.

Atrial Fibrillation. The onset of atrial fibrillation is accompanied by the loss of coordinated atrial contraction, which may have detrimental hemodynamic effects. Uncontrolled atrial fibrillation with rapid heart rate is particularly troublesome to patients with HF. Ventricular filling may be compromised further, myocardial oxygenation adversely affected and myocardial contractility diminished. Atrial flutter or tachycardia with a 2:1 AV block may masquerade as or be mistaken for sinus tachycardia.

Uncontrolled Hypertension. Uncontrolled hypertension is a very common finding in patients admitted with ADHF. Data from the ADHERE registry indicate that approximately 50% of patients admitted with this syndrome have blood pressure $>140/90$ mm Hg.[2] Hospitalization for ADHF provides another opportunity to add medication aimed at improving long-term control of hypertension. However, excessive dosing of antihypertensive medication during concomitant diuresis may result in symptomatic orthostasis.

Myocardial Ischemia/Infarction. The occurrence of myocardial ischemia and infarction are significant, potentially treatable precipitants of acute exacerbation of HF. Use of coronary angiography and noninvasive imaging to determine the presence and extent of myocardial ischemia is important in the evaluation of patients with acute as well as chronic HF. Patients with HF complicating acute coronary syndrome often require rapid coronary angiography and intervention in the catheterization laboratory. Considerations that determine the diagnostic approach toward ischemic heart disease are often similar in patients with acute and chronic HF (see Section 13).

Other Precipitants of Acute HF. A number of other factors, many of which are preventable or avoidable, may be primary or secondary causes of hospital admission for HF.

Right Ventricular (RV) Pacing. If the underlying heart rate slows over time in response to beta blockers or for other reasons, patients with RV pacemakers may pace more frequently. In some patients, the increase in RV pacing may lead to myocardial dysfunction, presumably from the dyssynchrony produced by the pacing.[144]

Pulmonary Disease. Even minor congestion may be poorly tolerated in the presence of chronic obstructive pulmonary disease (COPD) because volume expansion easily impairs the already limited pulmonary function in these patients. Both HF and COPD increase the risk of pulmonary infections, which can cause ADHF. Sleep disordered breathing may exacerbate HF through adverse hemodynamic changes, hypoxia and fluid retention.

Anemia. The presence of anemia has been associated with increased risk of admission for ADHF. The reduction in hemoglobin may be profound in cases where bleeding, especially gastrointestinal, is a cause, or end-stage renal disease is the principal mechanism.

Thyroid Diseases. Hypo- or hyperthyroidism may exacerbate the signs and symptoms of HF. Up to 20% of patients hospitalized for ADHF are already being treated for thyroid disease. Therefore, evaluation of patients' thyroid therapy is recommended. For patients taking amiodarone, worsening HF with emergence of tachyarrhythmias may be due to amiodarone-induced thyrotoxicosis.

Noncardiac Medications. A number of medications, both cardiac and noncardiac, can precipitate or contribute to an episode of worsening HF. Medications for diabetes, including pioglitazone or rosiglitazone, may lead to peripheral edema, which can be associated with adverse clinical and hemodynamic effects. Similar effects are seen with pregabalin, which is frequently used to treat diabetic neuropathy.[146] Nonsteroidal anti-inflammatory drugs and COX-2 inhibitors can promote sodium and fluid retention, interfere with the pharmacologic mechanism of ACE inhibitors, worsen renal function, and decrease the effectiveness of loop diuretics. Tricyclic antidepressants, whether used to treat depression or neuropathy, may cause cardiac conduction delays and increase the risk for ventricular arrhythmia. Theophylline and beta agonist bronchodilators may exacerbate HF by inducing tachyarrhythmias, including atrial fibrillation and flutter and ventricular arrhythmias. Over-the-counter drugs containing pseudoephedrine can aggravate hypertension, worsen HF by enhancing the activation of the sympathetic nervous system, and predispose to arrhythmias. Certain calcium antagonists and anti-arrhythmics may impair cardiac function and result in worsening HF.

Recommendation

12.24 It is recommended that every effort be made to use the hospital stay for assessment and improvement of patient adherence via patient and family education and social support services (see Section 8). (Strength of Evidence = B)

Background

Hospital admission provides the opportunity to educate patients concerning their HF and to reinforce both pharmacologic and non-pharmacologic approaches to management. Education in the hospital should be focused, because retention may be limited. Particular attention should be paid to the basic facts of HF, monitoring of fluid status, and medications. Identifying patients with limited social and family support before discharge may promote the development of a support system. Establishing support systems for patients with financial constraints is critical to their ability to obtain prescribed medications and access follow-up care. In a randomized, controlled trial of 233 hospitalized HF patients, a 1-hour pre-discharge teaching session directed by a nurse educator improved clinical outcomes and reduced cost of care.[64]

Hospital Discharge

Recommendation

12.25 It is recommended that criteria in Table 12.7 be met before a patient with HF is discharged from the hospital. (Strength of Evidence = C)

In patients with advanced HF or recurrent admissions for HF, additional criteria listed in Table 12.7 should be considered. (Strength of Evidence = C)

Background

Criteria for determining the optimal length of stay for individual patients admitted with ADHF remains to be established by rigorous clinical studies. Care must be taken to avoid premature discharge of patients with decompensated HF. The discharge criteria recommended here balance the need for adequate symptom relief and acceptably low readmission rates against the need for economical care.

Timing of discharge is further complicated by the fact that assessment of volume status can be difficult. As a result, patients with persistent volume overload are sometimes released prematurely. Patients who require several days of intravenous

Table 12.7. Discharge Criteria for Patients With HF

Recommended for all HF patients	• Exacerbating factors addressed. • Near optimal volume status observed. • Transition from intravenous to oral diuretic successfully completed. • Patient and family education completed, including clear discharge instructions • LVEF documented • Smoking cessation counseling initiated • Near optimal pharmacologic therapy achieved, including ACE inhibitor and beta blocker (for patients with reduced LVEF), or intolerance documented (Sections 7 and 11) • Follow-up clinic visit scheduled, usually for 7-10 days
Should be considered for patients with advanced HF or recurrent admissions for HF	• Oral medication regimen stable for 24 hours • No intravenous vasodilator or inotropic agent for 24 hours • Ambulation before discharge to assess functional capacity after therapy • Plans for postdischarge management (scale present in home, visiting nurse or telephone follow up generally no longer than 3 days after discharge) • Referral for disease management, if available

medications need a period of observation free of such support before discharge. In most cases, stability for 24 hours after discontinuation of intravenous therapy is sufficient to assess the likelihood that the patient will continue symptomatic improvement on oral medications alone. Meeting all criteria for discharge should be more stringently enforced in patients with advanced HF, especially the elderly, because they are at highest risk for readmission. Observation for a period of 24 hours after discontinuation of vasoactive or inotropic support is ideal, but shorter periods may suffice for patients whose symptoms have significantly improved and who tolerate weaning of intravenous support well.

Patients likely to need home care should have these plans developed and implemented before discharge. The hospital setting generally provides more resources for establishing this type of care plan than are available in outpatient settings.

Recommendation

12.26 Discharge planning is recommended as part of the management of patients with ADHF. Discharge planning should address the following issues:

- **Details regarding medication, dietary sodium restriction, and recommended activity level**
- **Follow-up by phone or clinic visit early after discharge to reassess volume status**
- **Medication and dietary adherence**
- **Alcohol moderation and smoking cessation**
- **Monitoring of body weight, electrolytes and renal function**
- **Consideration of referral for formal disease management. (Strength of Evidence = C)**

Background

The risk of readmission is highest just after hospitalization. Careful monitoring of patients soon after discharge may be useful in limiting the likelihood of readmission. Some patients have a tendency to become rapidly congested following discharge. Follow-up soon after discharge, either by phone or clinic visit, provides the opportunity to rapidly reevaluate the patient's volume status and to modify therapy to maintain control of congestion. It may be difficult to discharge patients on the dose of diuretic they probably need to maintain a euvolemic state after discharge when they have experienced a significant loss of fluid and have been maintained on a low sodium diet while in the hospital.

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Section 13: Evaluation and Therapy for Heart Failure in the Setting of Ischemic Heart Disease

Overview

In the United States (US) it is estimated that 16,800,000 people have a history of coronary heart disease, including myocardial infarction (MI), angina pectoris, or both.[1] The most common cause of chronic heart failure (HF) is no longer hypertension or valvular heart disease; it is coronary artery disease (CAD).[2] The changing pattern in the risk factors for HF is evidenced in the Framingham Heart Study, which documents a decrease in valvular disease and left ventricular (LV) hypertrophy and an increase in MI from 1950 to 1998.[3] As survival from MI continues to improve, it is expected that the number of patients with CAD and HF will also increase.

In 25 multicenter HF treatment trials reported in the *New England Journal of Medicine* over the past 20 years, involving more than 45,000 patients, CAD was present in nearly 65%.[4–29] This figure probably underestimates the true prevalence of CAD among unselected HF patients, because the presence of CAD was not explored systematically in many trials.

Prognostic Significance of Underlying CAD Etiology in Patients with HF

Several studies have shown that CAD is associated with an increase in mortality rates in patients with HF.[30–36] One study assessing angiographic data in patients with HF demonstrated that the extent of CAD in patients with HF and reduced left ventricular ejection fraction (LVEF) provides important prognostic information.[37] Data also suggest that the mechanism of sudden death may differ between ischemic and nonischemic HF patients, with acute coronary events representing the major cause of sudden death in HF patients with CAD.[38] In the Organized Program to Initiate Lifesaving Treatment in Hospitalized Patients with Heart Failure (OPTIMIZE-HF) registry, CAD was associated with higher in-hospital and post-discharge mortality compared to patients without CAD.[33] In the Candesartan in Heart Failure Assessment of Reduction in Mortality and Morbidity (CHARM) trial, patients who experienced an acute coronary syndrome (ACS) during follow-up had a significantly increased risk of death as compared to those who did not experience an ACS.[39] These findings further emphasize the importance of accurate differentiation between ischemic and nonischemic causes of HF.

Managing HF in patients with CAD or a history of CAD may be significantly different than managing HF due to primary cardiomyopathy. Antiplatelet agents, smoking cessation, and lipid-lowering therapy are particularly important interventions in patients with HF due to CAD.[40] Trials of milrinone,[41] amiodarone,[18] amlodipine,[15] and digoxin suggest that patients with HF in the setting of CAD may have a less favorable outcome than patients with HF from primary cardiomyopathy. Revascularization in highly selected patients with reduced LVEF and significant CAD, particularly those with anginal symptoms, may be associated with improved survival and may be considered in addition to risk modification.[33,42–49] No prospective randomized trials of coronary artery bypass surgery have been completed in patients with clinical HF, although the ongoing Surgical Treatment for Ischemic Heart Failure (STICH) and the Heart Failure Revascularization Trial (HEART) studies should clarify the role of revascularization in this population.[50,51]

Pathophysiology of HF in the Setting of CAD. HF in the setting of CAD is a heterogeneous condition with several factors contributing to LV systolic dysfunction and HF symptoms. After an MI, there is loss of functioning myocytes, development of myocardial fibrosis, and subsequent LV remodeling, resulting in chamber dilatation and neurohormonal activation-all leading to progressive dysfunction of the remaining viable myocardium.[49] This well-recognized process may be ameliorated after an acute MI by myocardial revascularization[47,49,52–55] and by medical therapy with angiotensin-converting enzyme (ACE) inhibitors, angiotensin receptor antagonists (ARBs),[56,57] beta blockers,[58] and aldosterone antagonists.[59]

The majority of patients surviving a MI have significant atherosclerotic disease in coronary arteries other than the infarct-related vessel.[60] Under basal conditions, episodes of reversible myocardial ischemia caused by a severe coronary artery stenosis superimposed on the left ventricle with depressed LVEF may produce transient worsening of LV function. In many patients, HF symptoms, such as dyspnea or fatigue induced by exercise, may represent an anginal equivalent.

Episodes of transient myocardial ischemia may cause prolonged systolic dysfunction that persists after the ischemic insult itself has resolved. This process, called stunning, is similar to the more severe and protracted myocardial stunning that results from coronary occlusion and reperfusion.[61]

Another important mechanism for systolic dysfunction with additive effects on LV performance is myocardial hibernation,[62] a process in which myocardial contraction is reduced in response to chronic reduction in myocardial blood supply.[63,64] More than 50% of patients with HF and CAD have evidence of viable but dysfunctional (hibernating) myocardium.[65,66] Hibernation may develop as an adaptive response to sustained reduction of myocardial blood flow. Thus, the level of tissue perfusion is sufficient to maintain cellular viability but insufficient for normal contractile function.[67] Recent evidence supports the long-held concept that hibernation represents a precarious balance between perfusion and tissue viability that cannot be

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maintained indefinitely, and that myocardial necrosis will occur eventually if blood flow is not increased.[62]

In addition to ischemia, hibernating myocardium should be considered in all patients with CAD and chronic LV systolic dysfunction of any degree.[68] Hibernating myocardium can be identified using low-dose dobutamine stress echocardiography to assess contractile reserve, single photon emission tomography with thallium-201 or technetium-99m perfusion tracers to assess membrane integrity, and positron emission tomography (PET) to assess residual metabolic activity.[69,70] Magnetic resonance imaging (MRI) has also been used to identify potentially viable but dysfunctional myocardium.[71]

Identification of hibernating myocardium is important, as the restoration of blood flow by revascularization or with agents that improve endothelial function and blood flow (eg, statins) may improve contractility in hibernating areas.[72–75] However, it should be noted that current testing modalities are limited in their ability to identify areas that will recover with revascularization.

Evaluation for CAD

Recommendations

13.1 Ongoing assessment for risk factors for CAD is recommended in all patients with chronic HF regardless of LVEF. (Strength of Evidence = A)

13.2 It is recommended that the diagnostic approach for CAD be individualized based on patient preference and comorbidities, eligibility, symptoms suggestive of angina and willingness to undergo revascularization. (Strength of Evidence = C)

13.3 It is recommended that patients with HF and symptoms suggestive of angina undergo cardiac catheterization with coronary angiography to assess for potential revascularization. (Strength of Evidence = B)

13.4 It is recommended that, at the initial diagnosis of HF and any time symptoms worsen without obvious cause, patients with HF, no angina, and known CAD should undergo risk assessment that may include noninvasive stress imaging and/or coronary angiography to assess severity of coronary disease and the presence of ischemia. (Strength of Evidence = C)

13.5 It is recommended that patients with HF, no angina, and unknown CAD status who are at high risk for CAD should undergo noninvasive stress imaging and/or coronary angiography to assess severity of coronary disease and the presence of ischemia. (Strength of Evidence = C)

13.6 In patients with HF, no angina, and unknown CAD status who are at low risk for CAD noninvasive evaluation should be considered and coronary angiography may be considered. (Strength of Evidence = C)

13.7 Any of the following imaging tests should be considered to identify inducible ischemia or viable myocardium:
- **Exercise or pharmacologic stress myocardial perfusion imaging**
- **Exercise or pharmacologic stress echocardiography**
- **Cardiac magnetic resonance imaging (MRI)**
- **Positron emission tomography scanning (PET) (Strength of Evidence = B)**

Background

Evaluation for CAD in Patents with HF. Multiple studies have evaluated the impact of nuclear viability imaging on intermediate to long-term survival in patients with CAD and LV systolic dysfunction.[76-89] However, none of these studies met the criteria published by the Evidence-Based Medicine Group on therapeutic interventions and prognosis.[90,91] In these studies treatment allocation to revascularization or medical therapy was often made by physicians who requested and, in some cases, interpreted the viability tests. Viability was never blindly evaluated without impacting subsequent treatment allocation. A randomized clinical trial is necessary to properly evaluate the utility of viability imaging to determine treatment allocation between revascularization and medical therapy and subsequent prognosis.

Recommendation

13.8 It is recommended that the following risk factors be managed according to the indicated guidelines:
- **Lipids (see National Cholesterol Education Program Adult Treatment Panel III) (http://www.nhlbi.nih.gov/guidelines/cholesterol)** [92,93]
- **Smoking (see Section 3)**
- **Physical activity (see Section 6)**
- **Weight (see Section 3)**
- **Blood pressure (see Section 14 and JNC VII Guidelines) (http://www.nhlbi.nih.gov/guidelines/hypertension)** [94]

Background

For more information on lipid management, smoking cessation, weight management, and physical activity see Sections 3 and 6 in this guideline.

Therapy for Patients With HF and CAD

Recommendation

13.9 Antiplatelet therapy is recommended to reduce vascular events in patients with HF and CAD unless contraindicated. (aspirin, Strength of Evidence = A; clopidogrel, Strength of Evidence = B)

Background

Aspirin. In patients with stable CAD, unstable angina or acute MI, treatment with aspirin 81−325 mg daily provides a 25% to 30% reduction in all-cause mortality, MI, and stroke.[95] In a retrospective review of the Studies of Left Ventricular Dysfunction (SOLVD) trial, antiplatelet use (mostly aspirin) was associated with 28% reduction in all-cause mortality and HF death or hospitalizations.[96] Despite conflicting data about aspirin reducing the benefits of ACE inhibitors,[96,97] all patients with CAD and HF should receive 75−325 mg aspirin daily in absence of contraindications. Recent studies suggest that higher doses may be associated with increases in drug interactions and bleeding, so 75 to 81 mg is recommended. (See Section 7, Recommendations 7.33−7.38.)

In the Warfarin and Antiplatelet Therapy in Chronic Heart Failure (WATCH) trial, patients with symptomatic heart failure, LV dysfunction, and no atrial fibrillation, were randomized to aspirin 162 mg/day, clopidogrel 75 mg/day, or open-label warfarin to achieve an international normalized ratio (INR) of 2.5 to 3.[98] The primary endpoint of the study was the composite of all-cause mortality, non-fatal MI, and non-fatal stroke. The majority of patients had an ischemic etiology of heart failure, although the study population was not limited to patients with CAD. There were no statistically significant differences in the primary endpoint for warfarin versus aspirin, for clopidogrel versus aspirin, or for warfarin versus clopidogrel.[98]

Clopidogrel. In patients admitted for unstable angina/non ST-elevation MI (STEMI), treatment with clopidogrel in addition to aspirin was associated with an 18% reduction in the incidence of HF.[99] All patients admitted with ACS and non-ST elevation treated medically without stenting should be given clopidogrel 300 mg, followed by 75 mg daily for at least 1 month and ideally for up to 1 year in addition to aspirin.[100] Patients with STEMI should be treated with clopidogrel or prasugrel, according to the 2009 STEMI/percutaneous coronary intervention (PCI) Focused Update Recommendations.[101]

Warfarin. Although warfarin is an acceptable alternative to antiplatelet agents when necessary for CAD, its effectiveness may be due to the large number of HF patients with atrial fibrillation. It was not superior to aspirin in the WATCH trial.[100] See Section 7 for more information.

Recommendation

13.10 ACE inhibitors are recommended in all patients with either reduced or preserved LVEF after an MI. (Strength of Evidence = A)

Background

In a study of patients with stable CAD and few other risk factors, treatment with the ACE inhibitor perindopril was associated with a 20% reduction in cardiovascular mortality, new MI, or sudden death.[102] HF hospitalizations were reduced by 39%. In a population at high risk for CAD, but without overt HF, treatment with ramipril was associated with a 22% reduction in cardiovascular mortality, new MI, or stroke.[103] The incidence of HF was reduced by 23% and HF hospitalizations by 12%. ACE inhibitors should be routine therapy in patients at high-risk for CAD and in patients with established CAD.

Four major trials proved the favorable effects of prophylactic ACE inhibition in reducing HF, HF hospitalizations and mortality after an acute MI.[104−107] In patients with a recent MI, with or without symptoms of HF, ACE inhibitors should be started early (within 24 hours) and continued indefinitely.[108]

The first trial to show a survival benefit for ACE inhibitors in patients with chronic HF, of whom the majority had underlying CAD, was the Cooperative North Scandinavian Enalapril Survival Study (CONSENSUS) trial. This trial was conducted in New York Heart Association (NYHA) class IV patients who were randomized to receive enalapril or placebo.[20] At the end of the study (20 months), patients treated with enalapril had a significant 27% reduction in total mortality, the primary end point. It appeared that enalapril had no effect on sudden death, but decreased mortality from progressive HF by 50%. After CONSENSUS, the SOLVD Treatment trial examined the effect of enalapril in patients with mild to moderate HF.[109] Enalapril decreased all-cause mortality by 16%, mortality caused by progressive HF by 22%, and the combined point of death or hospitalizations for worsening HF by 26% compared with placebo. In the SOLVD Prevention trial of patients with asymptomatic LV dysfunction, enalapril reduced the total number of deaths and cases of HF by 29%.[22] Taken together, these studies provide for the recommendation that ACE inhibitors should be administered to all patients with asymptomatic LV systolic dysfunction or with signs and symptoms of HF.

Recommendations

13.11 Beta blockers are recommended for the management of all patients with reduced LVEF or post-MI (Strength of Evidence = B)

13.12 It is recommended that ACE-inhibitor and beta blocker therapy be initiated early (<48 hours) during hospitalization in hemodynamically stable post-MI patients with reduced LVEF or HF (Strength of Evidence = A)

Background

In patients with stable CAD, treatment with beta blockers is associated with a reduction in the number and duration of ischemic episodes, mortality or hospitalization.[110] Retrospective analyses of two large beta blocker trials demonstrated reduced mortality with beta blockers, especially in

high-risk subsets.[111,112] In the Carvedilol Post-Infarct Survival Control in Left Ventricular Dysfunction (CAPRICORN) trial of 1959 patients with a proven acute MI and LVEF ≤40%, with or without symptoms of HF, carvedilol reduced the number of deaths by 23%, a benefit attained on top of treatment with ACE inhibitors, antiplatelet agents, and statins.[58] There was no difference between carvedilol and placebo in the number of patients meeting the primary endpoint of all-cause mortality or hospital admissions. In all patients with a history of MI, regardless of LVEF, beta blockers should be used acutely and continued indefinitely. In studies of patients with chronic HF, more than 65% of whom had underlying CAD, use of bisoprolol, carvedilol, or metoprolol succinate was associated with a uniform 34% reduction in all-cause mortality and 20% to 25% reduction in hospitalizations.[16,113,114] In the Australia-New Zealand study of patients with ischemic cardiomyopathy and LVEF <45%, carvedilol reduced the risk of all-cause mortality or any hospitalization by 26%.[115] Based on the results from available studies, beta blockers should be routinely prescribed to all patients with asymptomatic LV dysfunction and stable HF caused by LV systolic dysfunction.

Recommendation

13.13 Nitrate preparations should be considered in patients with HF when additional medication is needed for relief of anginal symptoms. (Strength of Evidence = B)

Background

In patients with stable CAD, nitrates improve exercise tolerance and time to onset of angina.[116] An overview of small studies of nitrates in acute MI from the pre-thrombolytic era suggested a 35% reduction in mortality rates,[117] although 2 trials formally tested this hypothesis in patients with suspected acute MI and failed to confirm this magnitude of benefit.[118,119] There was no difference in survival in the 14% of patients with HF at baseline in the Fourth International Study of Infarct Survival (ISIS-4) trial, nor was there a difference in the new cases of HF in Gruppo Italiano per lo Studio della Sopravvivenza nell-infarto Miocardio (GISSI-3) study. Nitrates did not decrease the rate of re-infarction, but they decreased the rate of post-infarct angina in GISSI-3, in which nitrates in combination with lisinopril also decreased all-cause mortality by 17%. The difference was mainly attributable to the lower numbers of deaths and cases with LVEF ≤35%. Nitrates are well tolerated in acute MI and appear safe to use early in acute MI for symptomatic relief of angina or for reduced LVEF. Patients with CAD, HF, and anginal symptoms should be considered for therapy with nitrates in addition to beta blockers.

Recommendation

13.14 Calcium channel blockers may be considered in patients with HF who have angina despite the optimal use of beta blockers and nitrates. Amlodipine and felodipine are the preferred calcium channel blockers in patients with angina and decreased systolic function. Based on available data, first generation calcium channel blockers (i.e. diltiazem, verapamil) should be avoided in patients with CAD, HF, and LVEF <40, unless necessary for heart rate control or other indications. (Strength of Evidence = C)

Background

Although all calcium antagonists have anti-ischemic properties, a meta-analysis of 16 trials that used immediate-release and short-acting nifedipine in patients with MI and unstable angina reported a dose-related excess mortality.[120] First-generation calcium antagonists, such as diltiazem and nifedipine, were found to exacerbate HF or increase mortality in patients after MI with pulmonary congestion or an LVEF <40%.[121] An alternative consideration regarding the worsening of heart failure in early calcium channel blocker trials is reflex neurohormonal activation. It is possible that the earlier-generation calcium channel blockers would not have proved deleterious if they had been investigated on a background of ACE inhibitors and beta blockers. Amlodipine does not have clinically significant negative inotropic effects, and it has not been associated with the deleterious effects seen with earlier drugs in this class. Although one trial of amlodipine in patients with advanced HF produced a 9% reduction in the combined risk of fatal and nonfatal events and decreased the risk of all-cause mortality by 16%, these reductions were not statistically significant overall or for patients with ischemic heart disease.[15] Amlodipine had no effect on the frequency of worsening HF associated with hospitalizations or the rate of MI, but the amlodipine group had a higher incidence of pulmonary and leg edema, as well as renal failure.[15] Based on available data, first-generation calcium channel blockers should not be used in patients with CAD, HF and LVEF <40%. Amlodipine or felodipine could be used in these patients to manage angina or hypertension if beta blockers or nitrates are not tolerated.[122,123]

Recommendations

13.15 It is recommended that coronary revascularization be performed in patients with HF and suitable coronary anatomy for relief of refractory angina or ACS. (Strength of Evidence = B)

13.16 Coronary revascularization with coronary artery bypass surgery or percutaneous coronary interventions (PCI) as appropriate should be considered in patients with HF and suitable coronary anatomy who have demonstrable evidence of myocardial viability in areas of significant obstructive coronary disease or the presence of inducible ischemia. (Strength of Evidence = C)

Background

Despite advances in medical therapy, patients with severe CAD and symptomatic reduced LVEF have poor outcomes when treated medically.[14,16,17,20,30–36,58,59,102–109,113,114,124,125] Although revascularization for patients with CAD and HF seems the logical approach because restoration of blood flow may improve LV function and possibly survival,[73,74] there are no randomized controlled trials comparing revascularization with medical therapy to improve outcomes in patients with HF, demonstrated myocardial viability, and an LVEF $<35\%$. Revascularization of viable myocardial segments could provide benefit by improving contractility or by preventing additional myocardial remodeling.[126,127] Myocardial viability has been assessed by PET, single-photon emission computed tomography (SPECT), dobutamine echocardiography, and MRI. Registry and cohort studies provide some data for this group of patients. These data suggest that exercise capacity and HF symptoms improve after revascularization and the improvement is related to the amount of abnormal but viable myocardium.[126,128,129] Improvement in LVEF also is directly related to the amount of viable myocardium.[128,130] Finally, in non-randomized, observational studies, revascularization has been associated with improved survival compared to medical therapy in patients with myocardial viability and an LVEF $<35\%$.[69,128]

The results of medical therapy for both HF and CAD have improved markedly. It is impossible to estimate whether revascularization in well-treated HF patients will improve survival or clinical course. As a result, prospective randomized trials of revascularization in addition to optimal medical therapy compared to optimal medical therapy alone in patients with CAD, depressed LV systolic function, and symptoms of HF are necessary. At present, two such studies are underway.[50,51] In the interim, when PCI or surgical intervention is considered, the decision should be made in the context of the patient's functional status, prognosis, and surgical risk. See Section 10, recommendation 10.1 for further information.

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Section 14: Managing Patients with Hypertension and Heart Failure

Overview

Blood pressure is a simple measurement that assesses the interaction of heart function with vascular impedance. When heart function is normal, the impedance is the main determinant of blood pressure. Therefore, pressure (systolic and mean) becomes a powerful risk factor for development of left ventricular (LV) hypertrophy, increased myocardial oxygen consumption, coronary atherosclerosis, and subsequent heart failure (HF).[1,2] Control of blood pressure in this setting is critical to prevent the development and progression of LV dysfunction.[3]

When LV function is impaired, however, the relationship between impedance and cardiac function becomes more complex. Increases of impedance may impair LV emptying and thus not be reflected in a higher pressure. Under those circumstances therapy is aimed at the impedance, not at the blood pressure. Indeed, blood pressure may rise in response to effective therapy that improves LV emptying or reverses remodeling even if the impedance is reduced.

Recommendation for Patients with Hypertension and Preserved Left Ventricular Ejection Fraction (LVEF) and Asymptomatic Left Ventricular Hypertrophy (LVH), or for Patients with Hypertension and HF with Preserved LVEF (Stage B)

14.1 It is recommended that blood pressure be optimally treated to lower systolic and usually diastolic levels. More than 1 drug may be required. Target resting levels should be <130/<80 mm Hg, if tolerated. (Strength of Evidence = A)

Recommendations for Patients with Hypertension and Asymptomatic LV Dysfunction With LV Dilation and a Low LVEF

14.2 Prescription of an angiotensin converting enzyme (ACE) inhibitor (dose equivalent to 20 mg daily enalapril) is recommended (Strength of Evidence = A)

14.3 Addition of a beta blocker (dose equivalent to HF trials) is recommended even if blood pressure is controlled. (see Table 7.1) (Strength of Evidence = C)

14.4 If blood pressure remains >130/80 mm Hg then the addition of a thiazide diuretic is recommended, followed by a dihydropyridine calcium antagonist (eg, amlodipine or felodipine) or other antihypertensive drugs. (Strength of Evidence = C)

Recommendations for Patients with Hypertension and Symptomatic LV Dysfunction With LV Dilation and Low LVEF

14.5 Prescription of target doses of ACE inhibitors, angiotensin receptor blockers (ARBs), beta blockers, aldosterone inhibitors, and isosorbide dinitrate/hydralazine in various combinations (with a loop diuretic if needed) is recommended, based on doses used in large-scale outcome trials (see Table 7.1). (Strength of Evidence = A)

14.6 If blood pressure remains >130/80 mm Hg, a dihydropyridine calcium antagonist (eg, amlodipine or felodipine) may be considered or other antihypertensive medication doses increased. (Strength of Evidence = C)

Background

Target Blood Pressure in HF. In hypertensive patients with evidence for LV dysfunction, therapy should be aimed at blood pressure reduction to the lowest levels that can be achieved without side effects, particularly when the LV dysfunction is associated with signs and symptoms of HF and preserved LV chamber dimension and LVEF. Most guidelines agree that a systolic pressure <130 mmHg or even lower may be optimal.[4–7] All effective antihypertensive drugs can reverse LV hypertrophy, but clinical trial data suggest that inhibition of the renin-angiotensin-aldosterone system with ACE inhibitors or ARBs may be most effective.[8,9] Adequate pressure reduction usually requires two or more drugs with different and complementary mechanisms of action.[5,6]

In hypertensive patients with HF and a dilated ventricle, therapy is aimed not predominantly at the pressure but at the vascular impedance and the cardiac structural remodeling.[10,11] Previously hypertensive patients respond similarly to drugs such as ACE inhibitors or ARBs, whether their pretreatment pressure is elevated, normal, or low.[12,13] In the patient population studied in the African-American Heart Failure Trial (A-HeFT), patients with lower systolic blood pressure (SBP) had a similar relative benefit from the use of isosorbide dinitrate/hydralazine as those with a higher SBP. The treatment did not reduce SBP that was already low.[14]

J-Shaped Curve. Several investigations suggest a link between excessive blood pressure lowering and an increased risk of clinical events. Data from the Hypertension Optimal Treatment (HOT) trial were modeled to evaluate the relationship between the level of blood pressure achieved and clinical risk.[13] In this analysis, more intensive diastolic blood pressure (DBP) lowering was associated with a lower risk of cardiovascular events among several subgroups, including diabetes, patients with ischemic heart disease, women, older patients, and patients classified as high or very high risk. In contrast, current smokers who

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achieved greater levels of DBP lowering (≤80 mmHg) had a higher risk of all types of cardiovascular events, except for myocardial infarction. These data minimize the clinical concern associated with lowering blood pressure, and suggest that the potential benefits on ventricular structure and function may outweigh the potential risks of a J-curve.

It is difficult to draw definitive conclusions about the existence of a J-curve and the optimal blood pressure for HF patients from these data derived in a non-HF hypertensive population; low blood pressure in HF patients, particularly in the acute setting, often reflects a low output state due to severe LV dysfunction, and may merely be a marker of poor outcome rather than a cause of poor outcome. Nonetheless, these data emphasize the need for more research to determine the optimal level of blood pressure for patients with HF.

Blood Pressure Change and Outcome in HF. Reviewing the data concerning the relationship of blood pressure change to outcome in HF reveals a complex relationship. On the positive side, large ACE inhibitor trials demonstrate a reduction in cardiovascular events and an improvement in ventricular structure associated with modest reductions in blood pressure.[15–17] In the Studies of Left Ventricular Dysfunction (SOLVD) trial, patients who received enalapril had final measured blood pressures averaging 120/78 mmHg, 5/3 mmHg lower than the placebo arm. An echocardiographic substudy demonstrated improved ventricular structure and reduction in LV hypertrophy in symptomatic or asymptomatic patients with LV systolic dysfunction.[18]

However, agents demonstrated to lower blood pressure have not always conferred a mortality benefit, and the degree of blood pressure reduction has not necessarily correlated with the degree of clinical benefit. Strong mechanistic arguments can be made that in some cases these drugs were associated with other adverse effects that would be very likely to limit any benefit from blood pressure reduction. Neurohormonal activation may occur in response to rapid or excessive drops in blood pressure; agents that reduce blood pressure by direct vasodilation mechanisms without neurohormonal inhibitory effects may lack the ability to reduce morbidity and mortality.[19–23]

On the whole it appears that benefits of lowering blood pressure in hypertensive patients with asymptomatic and symptomatic LV dysfunction are dependent on the resting blood pressure and the type of agents used. Drugs that lower blood pressure and produce neurohormonal blockade have produced the best results. When such agents can be used with additional drugs that lower blood pressure further without neurohormonal activation, achievement of aggressive blood pressure goals seems likely to confer additional risk reduction in patients with HF.

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Section 15: Management of Heart Failure in Special Populations

Overview

Heart failure (HF) is a prevalent condition in women, African Americans, and the elderly of both sexes and any race. In the absence of contradictory data, the clinical recommendations based on trial data derived from predominately younger white male study populations have generally been applied equally to these groups. However, there are etiologic and pathophysiologic considerations specific to these groups that warrant attention if care and outcomes are to be optimized. Discussion in this section is based primarily on available data from subgroup analyses of randomized HF trials and the results of cohort studies. A substantial amount of the data on drug efficacy comes from studies of patients treated after a recent acute myocardial infarction (MI).

Although a significant number of women and elderly patients with HF have preserved left ventricular ejection fraction (LVEF) there are few evidence-based data to guide therapy in this group. Other special populations, ethnic groups such as Hispanics, Asians, American Indians, or Pacific Islanders, are important special populations but there are inadequate data currently available about HF management to discuss these groups individually. Asian, particularly Chinese, patients have been reported to have a high incidence of cough with angiotensin converting enzyme (ACE) inhibitors, although this finding was not confirmed in a larger study of perindopril.[1−3] Mitochondrial aldehyde dehydrogenase-2 is responsible for the bioactivation of nitroglycerin as well as the clearance of acetaldehyde.[4] A polymorphism of this enzyme is present in 30-50% of Asians, and it is associated with decreased efficacy of the anti-anginal effects of nitroglycerin and an inability to clear acetaldehyde resulting in flushing after alcohol ingestion. Thus, it is possible, though not tested, that the combination of hydralazine and isosorbide dinitrate may not be effective in a significant number of Asians with HF. No HF treatment data is currently available in Hispanics, although epidemiologic factors such as diabetes may be particularly important in this subgroup.

The recommendations that follow are specific for the elderly, African-Americans, and women with HF and abnormal systolic function, as there are substantial data concerning HF management in these subgroups.

Elderly Patients with HF

Clinical Characteristics and Prognosis. HF represents a significant and growing public health problem for the elderly. The progressive aging of the US population is well established[5] and has profound implications for the prevalence of cardiovascular disease-particularly HF. A number of studies have documented the substantial increase in the prevalence of this syndrome as age increases.[6] As with most illnesses in the elderly, HF is associated with higher rates of morbidity and mortality than in younger patients.[7,8] Among elderly patients hospitalized with HF, median survival is approximately 2.5 years, with 25% of patients dying within 1 year.[9]

Pathophysiology of HF in the Elderly. There are a number of well described changes in cardiovascular physiology which occur with aging. Resting systolic left ventricular (LV) function appears to be preserved, but perhaps at the expense of some LV enlargement.[10] A diminution of diastolic function has been documented in otherwise normal elderly individuals.[11] Exercise capacity declines with age, most likely from a combination of changes in cardiac and peripheral vascular factors, ventricular-vascular coupling and aortic distensibility.[12,13] With age, diastolic filling of the ventricle becomes more dependent on atrial contraction and ventricular volume changes with increasing cardiac output are significantly different than those seen in younger subjects.[14] Though these diverse cardiovascular changes tend to reduce exercise capacity, their impact on health and quality of life remains modest in most individuals compared to the detrimental effects of HF.

The presentation of HF may differ in elderly patients with HF. Although they commonly present with the classic symptoms of dyspnea and fatigue, the elderly are more likely than younger patients to present with atypical symptoms such as poor executive functioning, altered mental status, or depression.[15,16]

Recommendations

15.1 As with younger patients, it is recommended that elderly patients, particularly those age >80 years, be evaluated for HF when presenting with symptoms of dyspnea and fatigue. (Strength of Evidence = C)

15.2 Beta blocker and ACE inhibitor therapy is recommended as standard therapy in all elderly patients with HF due to LV systolic dysfunction. (Strength of Evidence = B) In the absence of contraindications, these agents are also recommended in the very elderly (age >80 years). (Strength of Evidence = C)

15.3 As in all patients, but especially in the elderly, careful attention to volume status, the possibility of symptomatic cerebrovascular disease, and the presence of postural hypotension is recommended during therapy with ACE inhibitors, beta blockers and diuretics. (Strength of Evidence = C)

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Background

Beta Blockers. Diminished response to catecholamine stimulation in elderly individuals has been shown by several investigators[17] and appears related to diminished number and activity of both $beta_1$ and $beta_2$ receptors.[18] However, the changes in response to the sympathetic nervous system do not mitigate the need for beta receptor antagonism in the elderly. The striking risk in the elderly of major morbidity and early mortality, combined with the substantial benefit derived from beta blockade, strongly supports the use of these agents as tolerated in elderly patients with symptomatic LV systolic dysfunction.

Conclusions from randomized placebo-controlled trials are limited concerning the efficacy of beta blockade in the elderly. However, a retrospective analysis of a study of metoprolol CR/XL, which enrolled patients up to age 80 and included a substantial subgroup of elderly patients, found a similar degree of morbidity and mortality reduction in patients 69 or older versus those younger than 69.[19,20] Observational studies of the outcome of elderly patients after MI have consistently shown substantial reductions in mortality when beta blockers are prescribed at discharge.[21-23] These studies have included octogenarians. The one randomized trial of beta blockers in an elderly population with HF (mean age 76) demonstrated a reduction of 14% in the combined endpoint of all-cause mortality or primary cardiovascular admission for the group on nebivolol.[24]

ACE Inhibitors. No randomized controlled trial has been conducted specifically to investigate the benefit of ACE inhibition in elderly patients. However, convincing evidence of the effectiveness of ACE inhibition in elderly patients is provided by the results of a trial in which the mean age was 70 and the reduction in mortality was 31% at 2 year and 27% at the end of the study for patients with LV dysfunction following MI treated with ACE inhibition.[23] Observational studies and a meta-analysis of post-MI patients with HF reinforce these findings,[25−27] though caution is necessary in extrapolating the results of post-MI studies to chronic HF.

Other Medications. In the absence of data to the contrary, other HF medications, including angiotensin receptor blockers (ARBs), aldosterone antagonists, and the combination of hydralazine/isosorbide dinitrate, should be considered as options for elderly patients with HF, keeping in mind the complications of polypharmacy in a population characterized by multiple comorbidities. In particular, older age is an independent risk factor for hyperkalemia when inhibitors of the renin-angiotensin aldosterone system (RAAS) are used alone or in combination.[28]

HF in Women

Clinical Characteristics and Prognosis. HF is common in women, and among the elderly the prevalence of HF is greater in women than in men.[29] A growing body of evidence has demonstrated significant differences in the clinical characteristics and prognosis of HF in women and men. Early results from the Framingham Heart Study pointed to a difference in prognosis between men and women with HF, with men having worse survival than women.[30−32] Subsequent findings from some HF databases have confirmed this observation in both a broad population of patients with HF and those at a very advanced stage.[31,33−35] These studies have suggested that women's survival advantage is etiology-dependent, with better outcomes noted when the primary cause is non-ischemic. Hypertension and diabetes carry with them significantly greater risk of subsequent HF in women compared to men.[36] For women with coronary artery disease but no symptoms of HF, diabetes confers particular risk for the subsequent development of HF.[37] Diabetes and coronary disease are also associated with excess mortality in women with HF and systolic dysfunction compared to men.[38]

Sex and Cardiovascular Pathophysiology. A number of experimental studies point to fundamental, sex-related differences in the nature and extent of myocardial hypertrophy and adaptation, which might account for the survival advantage for females.[39,40] Early studies of spontaneously hypertensive rats suggested that the adverse influence of hypertrophy on cardiac function was greater in male than in female rats.[41] A number of animal studies suggest sex-related differences in myocardial remodeling in response to a pressure load and after MI.[41−46]

Treatment Response. Recognition of the pathophysiologic and clinical differences between men and women with HF has raised concern that treatment response might differ as well. Results of individual controlled clinical trials, even of standard therapeutic agents for HF from systolic dysfunction, generally are inconclusive, because of the small number of women enrolled. Data from pooled analyses are equally sparse. Recommendations are made in the context of this limited database.

Recommendation

15.4 Beta blocker therapy is recommended for women with HF from:
- **symptomatic LV systolic dysfunction (Strength of Evidence = B)**
- **asymptomatic LV systolic dysfunction (Strength of Evidence = C)**

Background

Women are underrepresented in HF clinical trials, as they are in clinical studies of other cardiovascular diseases.[47] However, a review of the experience of women in several of the large-scale prospective mortality trials of beta blockade in patients with symptomatic LV dysfunction does suggest that women and men benefit to a similar degree.[48]

Similarly, a pooling of the mortality results from several other large trials showed strong evidence of a similar beneficial effect in women and men.[48,49] Given the absence of contrary data, the most prudent course is to recommend the routine use of beta blockade for HF in both women and men.

Recommendation

15.5 ACE inhibitor therapy is recommended as standard therapy in all women with symptomatic or asymptomatic LV systolic dysfunction. (Strength of Evidence = B)

Background

As with beta blockers, the available data on ACE inhibition suggest comparable effects in women and men with HF. A meta-analysis of large-scale HF and post-MI randomized trials demonstrated evidence of a mortality benefit of ACE inhibition in women. A more convincing effect was seen on the composite end point of death, reinfarction, or admission for HF. Comparable findings related to sex were also noted in the meta-analysis of mostly small-scale, short-term studies of ACE inhibition, which found similar favorable point estimates for reduction in mortality and for mortality plus hospitalization in women.[25,50]

Recommendation

15.6 ARBs are recommended for administration to symptomatic and asymptomatic women with an LVEF ≤40% who are intolerant to ACE inhibitors for reasons other than hyperkalemia or renal insufficiency. (Strength of Evidence = A)

Background

Investigators in both the Valsartan Heart Failure Trial (Val-Heft) and the Candesartan in Heart Failure Assessment of Reduction in Mortality and Morbidity (CHARM) trials have analyzed the benefits of valsartan and candesartan, respectively, in women with HF and systolic dysfunction. In Val-HeFT significant reductions in both morbidity and mortality and HF hospitalizations were reported for women and were the same as benefits reported in men.[51] In CHARM there was a significant reduction in all-cause mortality and HF hospitalization that was the same as in men.[38] Subgroup analysis of the Valsartan in Acute Myocardial Infarction Trial (VALIANT) study also showed no difference in the effects of ARB vs. ACE inhibitor in men and women status post MI complicated by HF, LV dysfunction or both.[52] Thus the recommendations for ARBs in women have a level of evidence similar to those for men. Cough due to ACE inhibitors is more than twice as common in women compared to men and thus substitution of ARBs for ACE inhibitors is also likely to be more common in women compared to men.[53]

Evidence for Other Medical Therapy in Women

Although digoxin therapy has been demonstrated to decrease HF hospitalization,[54] it has not been demonstrated to improve survival. In a retrospective analysis of the Digitalis Investigation Group (DIG) trial, digoxin was associated with an increased risk of death from any cause among women, but not men, with HF and reduced LVEF.[55] However, that analysis did not account for serum potassium concentration and serum digoxin concentration differences. Another analysis of the same trial reported no excess mortality in either women or men with digoxin at serum concentrations between 0.5 and 0.9 mg/ml.[56] This report demonstrated that digoxin levels are higher in women compared to men at any given dose presumably due to decreased lean body mass and renal function. Analysis of the Studies of Left Ventricular Dysfunction (SOLVD) trials also did not demonstrate an increase in mortality in women with digoxin.[57]

Although sex-specific data is not available from prospective trials on the benefits of aldosterone antagonists for women with LV systolic dysfunction and symptoms of HF, adequate numbers of women were included in the large randomized, controlled trials of these agents and subgroup analyses were shown to demonstrate benefit in women.[58,59]

Recommendation

15.7 The combination of hydralazine/isosorbide dinitrate is recommended as standard therapy for African American women with moderate to severe HF symptoms who are on background neurohormonal inhibition. (Strength of Evidence = B)

Background

The A-HeFT (African-American Heart Failure Trial) confirmed the benefit of hydralazine/isosorbide dinitrate in black HF patients.[60] Importantly, 40% of the A-HeFT cohort were women. An analysis of outcomes by gender in A-HeFT showed that fixed-dose combined hydralazine/isosorbide dinitrate improved HF outcomes in both men and women. There were no gender differences between men and women in the benefit of hydralazine/isosorbide dinitrate on the primary composite score, time to first HF hospitalization, and event-free survival.[61]

HF in African Americans

Clinical Characteristics and Prognosis. Cardiovascular disease is a major health issue for African Americans.[30,62] Traditionally, concern has focused on hypertension and stroke as key components of the burden of cardiovascular disease in this population. However, HF represents a major source of cardiovascular morbidity and mortality for African Americans. Epidemiologic data suggests that they are

at greater risk for HF than Caucasians, with approximately 3% of all African-American adults affected.

A number of clinical studies have documented substantial differences between the baseline clinical characteristics of African Americans and Caucasians with HF.[33,34,49] Age of onset is significantly younger in blacks than in whites, and HF is less likely to be due to ischemic heart disease. Incident HF before 50 years of age is substantially more common among blacks than among whites. Hypertension, obesity, and systolic dysfunction that are present before a person is 35 years of age are important antecedents.[63]

Analysis of outcome data from the SOLVD trials has shown higher mortality and morbidity rates in blacks compared to whites with HF.[64] Whether these differences reflect differences in baseline characteristics, delivery of care or socioeconomic factors has not been resolved. Other studies point to problems with access to care and unfavorable clinical characteristics independent of HF as factors increasing the risk of African Americans for worse outcomes.[65–67]

Aggressive, early treatment of hypertension has been proposed as a major strategy for the prevention of HF in this racial group. Persistent hypertension is not uncommon in African-American patients with HF and systolic dysfunction.

Treatment Response. Although a number of clinical characteristics have been shown to differ significantly between African Americans and other races afflicted with HF, the implications of these differences for therapy remain to be determined.

Recommendation

15.8 Beta blockers are recommended as part of standard therapy for African Americans with HF due to:
- **symptomatic LV systolic dysfunction (Strength of Evidence = B)**
- **asymptomatic LV systolic dysfunction (Strength of Evidence = C)**

Background

Although 1 trial with bucindolol did not find a beneficial effect of beta blockade in African Americans with HF,[68] subgroup analysis of data from the US Carvedilol Trials suggests that the beneficial effect of beta blockers on outcomes in African Americans with HF from systolic dysfunction is similar to the effects in the larger population.[69] Other studies demonstrate similar findings.[21,50,70] The totality of the data supports substantial benefit from these agents, regardless of race.

Recommendations

15.9 ACE inhibitors are recommended as part of standard therapy for African-American patients with HF from symptomatic or asymptomatic LV systolic dysfunction. (Strength of Evidence = C)

15.10 ARBs are recommended as substitute therapy for HF in African Americans intolerant of ACE inhibitors. (Strength of Evidence = B)

Background

ACE Inhibition. Long-standing clinical experience suggests that African Americans with hypertension respond less well than Caucasians to ACE inhibitors.[71] Concern has persisted that differences in the effectiveness of blockade of the RAAS in HF might be present between the 2 races as well. Recently, retrospective subgroup analysis of data from 2 randomized clinical trials has added support to the concept that the response of blacks and whites with HF and LV systolic dysfunction to ACE inhibition may differ. A reanalysis of the SOLVD Prevention and Treatment trials investigated the influence of race on the response to enalapril.[72] Unadjusted analysis in the matched-cohort indicated that enalapril reduced the risk of hospitalization for HF in white patients by 44%, whereas no significant benefit was seen in black patients. Adjusted analysis confirmed a beneficial effect on hospitalization risk for Caucasians, but not for African Americans. At 1 year, enalapril therapy was associated with a significant reduction in both systolic blood pressure and diastolic blood pressure in Caucasian patients, whereas no significant reduction was observed in African-American patients.

It must be remembered that this study was a post-hoc subgroup analyses of randomized studies that were not stratified based on race. The SOLVD data raise the possibility that treatment response to ACE inhibition may vary between the races. However, they do not provide sufficient data to support a strategy other than routine use of ACE inhibitors in African Americans with HF.

Clinical studies have also shown that the risk of angioedema is greater in African American patients compared to Caucasians.[73]

Angiotensin-Receptor Blockade. The use of ARBs in African Americans with HF has not been well characterized in clinical trials. It would thus be reasonable in this population to follow the general recommendations for the use of ARBs (see Section 7).

Recommendation

15.11 A combination of hydralazine and isosorbide dinitrate is recommended as part of standard therapy in addition to beta blockers and ACE-inhibitors for African Americans with LV systolic dysfunction and:
- **New York Heart Association (NYHA) class III or IV HF (Strength of Evidence = A)**
- **NYHA class II HF (Strength of Evidence = B)**

Background

A strong recommendation now exists for the addition of the fixed combination of isosorbide dinitrate and

hydralazine to the standard medical regimen for African Americans with HF. Data from the Vasodilator-Heart Failure Trial (VHeFT) I and II suggested that a racial difference in treatment response existed between white and black patients with symptomatic LV dysfunction treated with hydralazine-isosorbide dinitrate versus placebo or enalapril, respectively.[74] The A-HeFT enrolled 1050 self-identified black patients who had NYHA class III or IV HF with dilated ventricles and systolic dysfunction.[60] In this placebo-controlled, blinded, and randomized trial, subjects were randomly assigned to receive a fixed combination of isosorbide dinitrate plus hydralazine or placebo in addition to standard therapy for HF. The primary end point was a composite score made up of weighted values for death from any cause, a first hospitalization for HF, and change in the quality of life. The study was terminated early owing to a significantly higher mortality rate in the placebo group than in the group given the fixed combination of isosorbide dinitrate plus hydralazine. The mean primary composite score was significantly better in the group given isosorbide dinitrate plus hydralazine than in the placebo group, as were its individual components: 43% reduction in the rate of death from any cause, 33% relative reduction in the rate of first hospitalization for HF, and an improvement in the quality of life. A provocative retrospective analysis of the A-HeFT study suggests that fixed dose isorsorbide dinitrate and hydralazine have a mortality benefit in African-Americans in the absence of beta-blockers and ACE inhibitors, and that beta-blockers but not ACE inhibitors add significant additional mortality benefit.[75]

Other Medications. In the absence of data to the contrary, other HF medications, including diuretics, digoxin, and aldosterone antagonists should be considered as options for the African-American patient with HF.

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Section 16: Myocarditis: Current Treatment

Overview

Myocarditis is a distinct clinical entity with a wide variety of cardiac manifestations including heart failure (HF). Potential etiologies may include toxins, medications, physical agents and, most importantly, infections. The most common forms appear to be postviral in origin. The pathophysiology of myocarditis has been well established in animal models with myocardial damage due not only to direct infection, but also consequent to postinfectious, autoimmune-mediated myocardial inflammatory damage. In humans, ongoing myocardial inflammation may result in dilated cardiomyopathy, restrictive cardiomyopathy, or acute left ventricular (LV) failure without dilatation (fulminant myocarditis).

Myocarditis is histologically characterized by both an active inflammatory cellular infiltrate within the myocardium and associated myocyte necrosis (the Dallas pathologic criteria).[1] Although many clinicians and pathologists consider the Dallas criteria too restrictive, this classification has established uniform histologic criteria for diagnosis and has substantially reduced the wide variation in reported rates of this disease. While the inflammatory infiltrate is lymphocytic in more than 90% of cases, eosinophilic infiltration or giant cell formation may occasionally be seen. The clinical features of myocarditis are extremely varied, ranging from asymptomatic electrocardiographic abnormalities observed during viral Coxsackie B outbreaks in the community to severe dilated cardiomyopathy with fulminant HF leading to transplantation or death.[2] Myocarditis may also cause ventricular arrhythmias or heart block or mimic acute myocardial infarction.[3–4] Both acute and chronic dilated cardiomyopathies may result from inflammatory heart disease. The histologic differentiation of myocarditis from idiopathic dilated cardiomyopathy remains problematic, because several published series suggest no difference in long-term prognosis, regardless of the presence or absence of myocardial inflammation.[5,6] Nonetheless, many clinicians believe that myocarditis is a potentially reversible form of cardiomyopathy and continue to perform endomyocardial biopsy searching for its presence.

Controversy continues to surround the best approach to the management of patients considered to have myocarditis. The following recommendation is based on a review of available data from uncontrolled and controlled evaluations of immunomodulatory therapy for the treatment of myocarditis.

Recommendation

16.1 Routine use of immunosuppressive therapies is not recommended for patients with myocarditis. (Strength of Evidence = A)

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Background

Uncontrolled Studies. More than 20 uncontrolled trials have been reported during the past 15 years on the use of immunosuppressive agents in the treatment of biopsy-proven lymphocytic myocarditis.[1] Therapies have included prednisone alone, prednisone and azathioprine, prednisone and cyclosporine, and short courses of OKT3 and immunoglobulin. Virtually all immunosuppressive protocols can result in rapid histologic improvement or resolution of the inflammatory component of the disease. Unfortunately, little or no correlation exists between histologic improvement and ventriculographic improvement. Improvement in ventricular function has been reported to range from 0% to 100% of patients.[1,7,8] Furthermore, spontaneous variation in LV ejection fraction (LVEF) and improvement in acute dilated cardiomyopathy are now well-recognized features of all forms of new onset cardiomyopathy. Thus uncontrolled series cannot answer the question as to whether the improvement in ventricular function exhibited by some patients was actually due to treatment or spontaneous improvement in the disease itself.

Controlled Trials. Three randomized, placebo-controlled trials have been performed which examined the role of immunosuppressive therapy in the treatment of acute dilated cardiomyopathy or myocarditis. One study randomly assigned 102 patients with dilated cardiomyopathy to treatment with either prednisone (60 mg/day) or placebo for 3 months.[9] The trial concluded that prednisone had marginal clinical benefit and should not be administered as standard therapy for dilated cardiomyopathy patients. A major criticism of this trial was that only a small number of patients had histologically verified myocarditis. A second trial of 52 patients with recently diagnosed idiopathic dilated cardiomyopathy treated with either conventional therapy alone or in combination with prednisone reported an inflammatory response on endomyocardial biopsy in 23% of the overall population, 13% of whom had Dallas criteria myocarditis.[10] Immunosuppressed patients received 50 mg of prednisone daily for 2 weeks followed by a taper by 10 mg every 2 weeks until the drug was discontinued. Biopsy-documented myocarditis resolved in all patients within 3 months regardless of treatment modality. Survival at 24 months, the primary endpoint of the study, was 64 ± 12% for the prednisone-treated patients compared to 83 ± 8% for the untreated patients ($P = .57$). The presence of myocardial inflammation did not influence survival. Thus prednisone was determined to be ineffective in improving the primary end point in the study.

The Myocarditis Treatment Trial (MTT) examined immunosuppressive therapy consisting of prednisone and cyclosporine in 111 patients with histologically verified myocarditis and an LVEF <45% who were randomized to receive conventional therapy alone or combined with immunosuppression for 6 months.[11] The primary outcome measure was prespecified as change in LVEF at 28 weeks.

The majority of patients received prednisone and cyclosporine immunosuppressive treatment, because the azathioprine treatment limb was prematurely terminated from slow study enrollment. For the group as a whole, LVEF improved from 25% at baseline to 34% at 28 weeks. The mean change in LVEF did not differ between treatment groups. A higher LVEF at baseline, shorter duration of symptoms, but not the randomized treatment assigned, were positive independent predictors of improvement in LVEF at 28 weeks. There was no difference in survival between treatment groups; the mortality rate for the entire group was 20% at 1 year and 56% at 4.8 years. This study is the only sizable randomized trial specifically focused on treatment of patients with myocarditis. Unfortunately, prednisone and cyclosporine-based immunosuppressive therapy produced no clinical benefit.

High-dose gamma-globulin has been shown to be effective treatment for a variety of immunologically mediated diseases such as Kawasaki's disease. The use of intravenous immunoglobulin (2 g/kg) in 21 consecutive children treated for presumed acute myocarditis demonstrated a trend for improved survival in the immunoglobulin group compared to historical controls.[12] Small studies using intravenous immunoglobulin in adult patients have shown mixed results. In one study with of 10 patients with a mean age of 36 years (range19-60), all patients had New York Heart Association class class III or IV HF symptoms and an LVEF $<40\%$.[13] One patient died, whereas the remaining 9 patients were discharged; LVEF in the survivors increased from 24% to 41%. However, two other small studies suggest a benefit of immunoglobulin on LVEF.[14,15]

A prospective randomized multicenter trial of the use of immunoglobulin in patients with cardiomyopathy of less than 6 months duration and symptomatic HF submitted all patients to endomyocardial biopsy; however, only 16% of the 62 patients randomized had Dallas criteria myocarditis.[16] The immunoglobulin and placebo control population had identical survivals at one year (92% and 88% respectively), and increases in LVEF from 25% at baseline to 42% at the 12 month follow-up. Therefore, despite encouraging data from uncontrolled observations, immunoglobulin therapy does not provide benefit to patients with new-onset cardiomyopathy and myocarditis.

Increasing concerns have been raised concerning the ability to diagnose myocarditis by endomyocardial biopsy using the Dallas criteria exclusively. Of the 2233 patients considered candidates for inclusion in the MTT, only 214 were thought to have myocarditis as defined by the Dallas criteria. Of the 111 patients enrolled in the trial, only 64% were "confirmed" as having myocarditis after review by an expert panel of pathologists. Chow and Hauck performed serial myocardial biopsies on postmortem hearts of patients who had died of myocarditis.[17,18] Even with 5 biopsy samples, only two-thirds of patients studied would have had the diagnosis of myocarditis using the Dallas criteria. Others have demonstrated that even in the presence of viral RNA or DNA by polymerase chain reaction techniques, histologic myocarditis often is not confirmed.[19]

Two recent European investigators have added significantly to our understanding of histologic versus immunologic "myocarditis." Wojnicz defined myocarditis by upregulation of human leukocyte antigen by endomyocardial biopsy in 84 patients of a cohort of 202 with new onset cardiomyopathy.[20] Patients were randomized prospectively to immunosuppression or placebo. Although the rates of death, transplantation, or hospitalization were virtually identical in the immunosuppressed and placebo-treated patients, those with immunosuppression increased their LVEF from 24% to 36%, whereas the control group showed virtually no increase. Based on the Dallas criteria alone, only 8.3% of the patients studied had active myocarditis and 19% had borderline myocarditis. Frustaci demonstrated histologic myocarditis in 112 of 652 patients with new-onset cardiomyopathy submitted to myocardial biopsy.[19] Of the 112 patients with myocarditis, 41 displayed progressive deterioration despite usual medical therapy and were treated with immunosuppression (azathioprine and prednisone). Approximately half of the patients responded to immunosuppressive therapy. Responders increased their LVEF from 26% to 47% and demonstrated healed myocarditis on follow-up biopsies. The 20 nonresponders had progressive deterioration to dilated cardiomyopathy, with 5 deaths and 3 cardiac transplantations. Cardiac antibodies were demonstrated in 90% of those who responded, compared with absence of antibodies in non-responders. The patients who failed to respond displayed viral persistence (85%).

Clearly, patients with subacute myocarditis and new onset dilated cardiomyopathy and HF often improve spontaneously with standard HF management. It is becoming increasingly clear that the Dallas criteria, which rely exclusively on histologic inflammatory infiltrate and myocyte necrosis, may be underestimating the presence of immune-related myocardial dysfunction. Recent evidence suggests that we may be on the verge of identifying patients for whom immunosuppressive therapy would be beneficial by using other markers of immune upregulation, anticardiac antibodies, or the absence of viral persistence. These data are not yet strong enough to alter our current recommendations, but should be revisited as new data become available.

Recommendation

16.2 Endomyocardial biopsy should be considered in patients with an acute deterioration of cardiac function of unknown etiology who are unresponsive to medical therapy. (Strength of Evidence = B)

Background

There are distinct clinical pathologic forms of myocarditis in which endomyocardial biopsy establishes not only the diagnosis but prognosis and treatment options. These include fulminant myocarditis, giant cell myocarditis, chronic active myocarditis, eosinophilic myocarditis and myocardial sarcoid.

Fulminant myocarditis is characterized by an abrupt onset of profound HF within 1 month of a preceding clearly recognized viral illness.[21] Patients present with nondilated, thickened left ventricles with severe systolic dysfunction on echocardiography. Endomyocardial biopsy reveals unquestionable histologic Dallas criteria myocarditis. These patients usually recover spontaneously within 2 weeks with complete resolution of histologic myocarditis and normalization of ventricular function. Their long-term prognosis is excellent. These patients should not be treated with immunosuppressive therapy, but may require temporary support with intravenous positive inotropes and/or ventricular assist devices.

Patients with giant cell myocarditis present with rapidly progressive HF, complete heart block, and/or malignant ventricular arrhythmias.[22] Many patients have an associated autoimmune process. Biopsy reveals widespread serpiginous necrosis and multifocal inflammation with eosinophils, histiocytes, lymphocytes, and multinucleated giant cells. Patients with untreated giant cell myocarditis usually die within 3 months of presentation. There are preliminary data to suggest that high-dose immunosuppressive therapy may improve survival in this population.[23]

Patients with chronic active myocarditis have an indistinct onset.[24] They present with HF and mild LV dilation and systolic dysfunction. Endomyocardial biopsies reveal both ongoing active inflammation and fibrosis. Both processes progress over the course of the illness. Ultimately patients develop a restrictive cardiomyopathy with refractory HF, usually over 2 to 3 years.

Hypersensitivity to a number of standard drugs may result in an allergic myocarditis. This inflammation is characterized by peripheral eosinophilia and infiltration of the myocardium with lymphocytes, histocytes, and eosinophils. This form of myocarditis is rarely recognized premortem and should be suspected in patients with stable LV dysfunction who deteriorate inexplicably, particularly after the initiation of a new medication.[25]

Acute necrotizing eosinophilic myocarditis presents like fulminant myocarditis with acute onset associated with a rapid hemodynamic compromise and histologic myonecrosis and a dramatic increase in eosinophils. There are limited data related to this syndrome and while immunosuppressive therapy seems intuitive, there are no treatment trials to support the use of these agents.[26,27]

Guidelines have recently been released concerning the use of endomyocardial biopsy in the management of cardiovascular disease. Fourteen clinical scenarios are described with associated class of recommendations and level of evidence for each clinical vignette, many of which relate to the evaluation of possible myocarditis.[28]

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Section 17: Genetic Evaluation of Cardiomyopathy*

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Overview

Substantial progress has been made recently in understanding the genetic basis of cardiomyopathy. Cardiomyopathies with known genetic cause include hypertrophic (HCM), dilated (DCM), restrictive (RCM), arrhythmogenic right ventricular dysplasia/cardiomyopathy (ARVD/C) and left ventricular noncompaction (LVNC). HCM, DCM, and RCM have been recognized as distinct clinical entities for decades, while ARVD/C and LVNC are relative newcomers to the field. Hence the clinical and genetic knowledge for each cardiomyopathy varies, as do the recommendations and strength of evidence.

The evidence indicating that HCM has a genetic basis is extensive: HCM is now understood largely to be a genetic disease of contractile proteins, although less commonly, infiltrative etiologies may also be causative (Table 17.1). The evidence supporting a genetic basis for DCM, after other more common causes have been excluded (e.g., ischemic disease, hypothyroidism, cardiotoxic agents such as doxorubicin), is now substantial for familial dilated cardiomyopathy (FDC), where FDC is defined as DCM of unknown cause in two or more closely related family members (Table 17.2). However, whether sporadic DCM has a genetic basis remains an open question, especially when detectable familial disease has been clinically excluded by testing closely related family members. Thus, while some recommendations formulated for the genetic evaluation of cardiomyopathy, such as the need for family history, apply to all entities, other recommendations must be tailored to account for these differences. This is particularly relevant as these guidelines use the generic term 'cardiomyopathy' to imply possible familial or genetic cause, assuming that all other detectable causes of cardiomyopathy have been ruled out. As noted above, multiple non-genetic causes are possible for DCM.

Recent discoveries indicate that ARVD/C is largely caused by mutations in genes encoding proteins of the desmosome (Table 3). Although initially recognized predominantly in the right ventricle, left ventricular involvement in 20−40% of patients has prompted the change in nomenclature from ARVD to ARVD/C.[1]

Discovering the genetic basis of restrictive cardiomyopathy (RCM) has been more challenging, as RCM is much less common than DCM or HCM, and less commonly presents with familial disease (Table 17.3).

LVNC is an anatomic abnormality of left ventricular myocardial development: left ventricular compaction is incomplete, leaving deep trabeculations in the LV myocardium. LVNC was categorized as a specific type of cardiomyopathy by an expert panel in 2006[2], and some genetic association has been observed (Table 17.3). Although initially reported to be a rare condition associated with adverse outcome[3], more recent reports [4−6] have called into question those preliminary conclusions.[7] Three different echocardiographic criteria have been utilized for diagnosis.[6] These authors suggested that the diagnostic criteria for LVNC might be too sensitive. Because of the uncertainty of diagnostic standards leading to difficulty clarifying its phenotype, we suggest that the LVNC recommendations be limited to those individuals with only the most prominent disease.

This section organizes recommendations by cardiac phenotype, recognizing that there is substantial overlap among phenotypes and some mutations are associated with more than one phenotype. Because therapeutic decision-making is generally dictated by phenotype, this approach was considered most helpful for the clinician.

The available clinical genetics data for each of the cardiomyopathies varies greatly in content and quality, and thus the quality and certainty of genetic counseling information is also variable. The evidence that supports clinical genetic testing varies greatly. While analytic validity (the ability of the test to detect a mutation) is attainable with current methods, evidence to support clinical validity (the ability of the test to detect the condition) remains quite limited for most cardiomyopathies, the exception being HCM. A separate measurement, clinical utility, defines the global risks and benefits of any test, asking the all-important question: how will the genetic information, whether positive or negative, affect clinical decision-making for the patient or the patient's family? Clinical utility remains to be defined for all genetic testing of cardiomyopathies.

While each recommendation has been designed for adult and pediatric patients, many of the references used to formulate these recommendations have focused primarily on adults. A section devoted to pediatric genetic cardiomyopathies provides additional specific information.

Despite these limitations, recent progress makes it possible to propose recommendations for the genetic evaluation of cardiomyopathy. These recommendations will evolve and mature as more robust clinical genetics knowledge becomes available.

HFSA Guideline Approach to Medical Evidence for Genetic Evaluation of Cardiomyopathy

Because genetic testing is relatively new, randomized clinical trials demonstrating that performing the specific genetic test improves outcomes are not available. Thus, we have used a different format for strength of evidence for clinical validity which asks the question "Does the test correlate with the outcome of interest?"[8] The hierarchy of types of evidence includes the following:

Table 17.1. Genetic causes of hypertrophic cardiomyopathy

Gene*	Protein	OMIM**	frequency, familial***	frequency, sporadic**	Comments	Selected References
AUTOSOMAL Dominant HCM - genes encoding sarcomeric proteins						
MYH7	β-myosin heavy chain	160760	30–40%	30–40%	wide age range; severe LVH; heart failure, SCD	10,11,37,38
MYBPC3	myosin-binding protein C	600958	30–40%	30–40%	usually milder disease, although can be severe; some older onset	10,11,38,39
TNNT2	cardiac troponin T	191045	10–20%	10–15%	mild LVH; SCD more common	10,11,38,40
TPM	α-tropomyosin	191010	2–5%	?		10,11,38,39
TNNI3	cardiac troponin I	191044	2–5%	?		10,11,38,41
MYL2	myosin regulatory light chain	160781	rare	rare		42
MYL3	myosin essential light chain	160790	rare	rare		42
ACTC	cardiac actin	102540	rare	rare		43
TTN	titin	188840	rare	rare		44
MYH6	α-myosin heavy chain	160710	rare	rare		45
TCAP	titin-cap or telethonin	604488	rare	rare		46
HCM caused by metabolic/infiltrative disease						
PRAGK2	AMP-activated protein kinase subunit	602743	?	?	HCM, with WPW	47
GLA	α-galactosidase	300644	?	?	Fabry disease, X-linked	48
LAMP2	lysosome associated membrane protein 2	309060	?	?	Danon disease, X-linked	49

*Genes within each category are ordered by publication.
**OMIM is Online Mendelian Inheriitance in Man (accessed via http://www.ncbi.nlm.nih.gov/sites/entrez?db=omim.
***Rare denotes a frequency usually < 1%.

Strength A: The specific genetic test or clinical test has a high correlation with the cardiomyopathic disease of interest in reasonably large studies from multiple centers.

Strength B: The specific genetic test or clinical test has a high correlation with the cardiomyopathic disease of interest in small or single center studies.

Strength C: The specific genetic test or clinical test correlates with the cardiomyopathic disease of interest in case reports.

The criteria for clinical utility follow those used for overall strength of evidence in the other sections of this guideline (see Section 1), and pose the question, ''Does performing the test result in improved patient outcomes?''

Strength A: randomized, controlled, clinical trials. May be assigned on the basis of a single methodologically rigorous randomized trial.

Strength B: Cohort and case control studies. Post-hoc, subgroup analysis, and meta-analysis. Prospective observational studies or registries.

Strength C: Expert Opinion. Observational studies-epidemiologic findings. Safety reporting from large-scale use in practice.

However, as noted previously for clinical validity, randomized or controlled clinical trials or large cohort and case/control studies are seldom available from genetic cardiomyopathy studies. Hence the authors graded strength of evidence based upon the totality of information available.

Recommendation

17.1 A careful family history for ≥ 3 generations is recommended for all patients with cardiomyopathy.

Cardiomyopathy Phenotype	Strength of Evidence
Hypertrophic cardiomyopathy (HCM)	**A**
Dilated cardiomyopathy (DCM)	**A**
Arrhythmic right ventricular dysplasia (ARVD)	**A**
Left ventricular non-compaction (LVNC)	**A**
Restrictive cardiomyopathy (RCM)	**B**
Cardiomyopathies associated with extra-cardiac manifestations (Table 17.4)	**A**

Background

The family history, long established as an essential component of any medical evaluation, is particularly relevant for the cardiomyopathies.[9] The first goal of the family history is to ascertain if the cardiomyopathy is familial, and if

Table 17.2. Genetic causes of dilated cardiomyopathy

Gene*	Protein	OMIM	Frequency, familial**	Frequency, sporadic**	Comments***	References
AUTOSOMAL Dominant FDC						
Dilated cardiomyopathy phenotype						
ACTC	cardiac actin	102540	rare	rare		50–54
DES	desmin	125660	?	?		53,55–57
LMNA	lamin A/C	150330	7.3%	3.0%	5.5% overall (41/748, 6 studies, see text)	21-26,58–64
SGCD	δ-sarcoglycan	601411	rare	rare		56,65,66
MYH7	β-myosin heavy chain	160760	6.3%	3.2%	4.8% overall (22/455, 3 studies)	19,67–69
TNNT2	cardiac troponin T	191045	2.9%	1.6%	2.3% overall (15/644, 3 studies)	19,67,69–72
TPM1	α-tropomyosin	191010	rare	rare		73
TTN	titin	188840	?	?		74
VCL	metavinculin	193065	rare	rare		69,75
MYBPC3	myosin-binding protein C	600958	?	?		68
MLP/CSRP3	muscle LIM protein	600824	rare	rare		19,76
ACTN2	α-actinin-2	102573	?	?		77
PLN	phospholamban	172405	rare	rare		69,78,79
ZASP/LDB3	Cypher/LIM binding domain 3	605906	?	?		19,80
MYH6	α-myosin heavy chain	160710	?	?		45
ABCC9	SUR2A	601439				81
TNNC1	cardiac troponin C	191040	?	?		72
titin-cap TCAP	titin-cap or telethonin	604488	rare	rare		19,46
SCN5A	sodium channel	600163	?	?	2.3% overall (11/469, 2 studies)	82–84
EYA4	eyes-absent 4	603550	?	?		85
TMPO	thymopoietin	188380	?	?		86
PSEN1/PSEN2	presenilin 1/2	104311	?	?		87
X-LINKED FDC		300377				
DMD	dystrophin	300394				88,89
TAZ/G4.5	tafazzin	300394				90,91
AUTOSOMAL RECESSIVE FDC						
TNNI3	cardiac troponin I	191044	?	?		92

*Genes are ordered by publication year.
**Rare indicates less than 1%; frequencies are provided only with two or more publications.
***Overall frequencies may include studies that did not distinguish between familial and sporadic cases.

so, to identify those individuals who may be at risk. Because of reduced penetrance observed in some families with cardiomyopathy, a family history extending to at least 3 generations improves recognition that a cardiomopathy is inherited and helps define dominant or recessive transmission. Patients unprepared for a recitation of their family history may only provide general information suggestive of cardiovascular disease in their relatives. Not uncommonly, the cause of any cardiovascular condition resulting in hospitalization may be described as a 'heart attack,' as is the case with sudden cardiac death (SCD). Hence, when the diagnosis of cardiomyopathy is suggested, the patient should be requested to obtain additional information to confirm or exclude the cardiomyopathy diagnosis. Specific medical information pertinent to the patient's diagnosis should be sought regarding the patient's relatives. For example, in HCM or ARVD/C, targeted questions relating to SCD in teenagers and young adults should be sought. Increasingly, practitioners record a pedigree to illustrate the family history data.

When taking a family history it is imperative that the professional recording it make no a priori assumptions of which side of the family the disease originated[9] and should consider bilineal inheritance (transmission of a disease-causing mutation in the same or a different gene from both mother and father). In HCM, reports of large series of patients undergoing comprehensive genetic screening have shown compound or double mutations in 5%.[10–12] It has been suggested that some of these individuals may have had more severe disease related to a 'double-dose' effect incurred from the two mutations.[12]

A second goal, once a cardiomyopathy is suspected or proven to be familial, is to ascertain the inheritance pattern. Pedigree analysis is undertaken to determine if the inheritance is autosomal dominant or recessive, X-linked dominant or recessive, or mitochondrial[9] and thus provide an accurate risk assessment. Most genes known to cause cardiomyopathies are transmitted in an autosomal dominant manner. Autosomal dominant inheritance implies that only one copy of the mutation in needed to cause the disease phenotype and that each child has a 50% chance to inherit the mutation. For X-linked inheritance, the mutation is carried in a gene on the X-chromosome.

Expanding a family history beyond the 3rd generation and collecting medical data from relatives known or suspected to manifest clinical disease consistent with the

cardiomyopathy in question can be enormously informative. With additional family and clinical data, further analysis of the pedigree may suggest the age of onset, penetrance, lethality, response to treatment and other aspects of the condition. However, because obtaining a family history and related activities outlined above are time and effort intensive, busy practitioners may choose to refer patients with cardiomyopathy to centers expert in genetic cardiomyopathies. Such centers may also provide genetic counseling and genetic testing, compile clinical and genetic databases, and offer research opportunities that are essential for progress in the field.

Recommendation

17.2 Clinical screening for cardiomyopathy in asymptomatic first-degree relatives is recommended.

a.

Cardiomyopathy Phenotype	Strength of Evidence
Hypertrophic cardiomyopathy (HCM)	**A**
Dilated cardiomyopathy (DCM)	**A**
Arrhythmic right ventricular dysplasia (ARVD)	**A**
Left ventricular noncompaction (LVNC)	**B**
Restrictive cardiomyopathy (RCM)	**B**
Cardiomyopathies associated with extra-cardiac manifestations (Table 17.4)	**A**

b. Clinical screening for cardiomyopathy is recommended at intervals (see below) in asymptomatic at-risk relatives who are known to carry the disease-causing mutation(s). (Strength of Evidence = A)

c. Clinical screening for cardiomyopathy is recommended for asymptomatic at-risk first-degree relatives when genetic testing has not been performed or has not identified a disease-causing mutation. (Strength of Evidence = A)

d. It is recommended that clinical screening consist of:
- **History (with special attention to heart failure symptoms, arrhythmias, presyncope and syncope)**
- **Physical examination (with special attention to the cardiac and skeletal muscle systems)**
- **Electrocardiogram**
- **Echocardiogram**
- **CK-MM (at initial evaluation only)**
- **Signal Averaged ECG (SAECG) in ARVD only**
- **Holter monitoring in HCM, ARVD**
- **Exercise treadmill testing in HCM**
- **Magnetic resonance imaging in ARVD**

(Strength of Evidence =B)

e. Clinical screening for cardiomyopathy should be considered at the following times and intervals or at any time that signs or symptoms appear:

Cardiomyopathy Phenotype	Interval if genetic testing is negative and/or if clinical family screening is negative	Screening interval if a mutation is present	Strength of Evidence
Hypertrophic	Every 3 years until 30 years of age, except yearly during puberty; after 30 years if symptoms develop	Every 3 years until 30 years of age, except yearly during puberty; every 5 years thereafter	B
Dilated	Every 3–5 years beginning in childhood	Yearly in childhood; every 1–3 years in adults.	B
ARVD	Every 3–5 years after age 10	Yearly after age 10 to 50 years of age.	C
LVNC	Every 3 years beginning in childhood	Yearly in childhood; every 1–3 years in adults.	C
Restrictive	Every 3–5 years beginning in adulthood	Yearly in childhood; every 1–3 years in adults.	C

f. At-risk first-degree relatives with any abnormal clinical screening tests (regardless of genotype) should be considered for repeat clinical screening at one year. (Strength of Evidence = C)

Background

The basis for these extensive clinical screening recommendations (and the counseling and molecular recommendations in the sections that follow) is the fact that cardiomyopathy can be treated in almost all cases, improving survival and/or enhancing quality of life.[13,14] In contrast, many other genetic diseases have no useful medical treatment. Further, determining genetic risk of cardiomyopathy prior to disease presentation guides the recommendations for increased surveillance to detect early disease onset and medical intervention. All of these measures may delay disease presentation and progression, thereby avoiding advanced therapies such as cardiac transplantation, or averting the sequelae of life-threatening events, such as sudden cardiac death.[14]

Most cardiomyopathies are adult onset, and as is common for adult-onset genetic disease, show a variable age of onset and variable penetrance. Hence, clinical screening of first-degree relatives of adults diagnosed with cardiomyopathy is recommended, regardless of whether a disease-causing mutation has been identified in the index patient. Because of the variable age of onset, clinical screening repeated at intervals is recommended, even if clinical genetic

testing has not identified a disease-causing mutation in the family. If a disease-causing mutation is identified, the frequency of pre-symptomatic clinical screening in relatives known to be mutation carriers is recommended with increased frequency, as the probability of future disease is increased among carriers. Increased frequency of follow up clinical screening should also be undertaken for at-risk relatives if clinical screening has shown that the disease is familial, even if a mutation has not been found. This is because for genetic cardiomyopathy, familial disease strongly suggests genetic cause. Further, the sensitivity of genetic testing varies greatly (as noted in the background to Recommendation 17.3). Conversely, as the table above shows, if the clinical screening of first-degree relatives is negative, or a disease-causing mutation has not been identified, the intervals for clinical screening are recommended to be less frequent because of the reduced evidence of genetic risk.

The rationale for this latter recommendation, although reasonable, is based upon limited data. With clinical screening, whether the lack of clinical evidence of cardiomyopathy in first-degree family members is helpful to predict the presence or absence of genetic cause of the proband's cardiomyopathy has not yet been resolved. This is because of the variable age of onset and variable penetrance. Resolution of this issue will require data from additional large, rigorously designed clinical and genetic studies. Despite these uncertainties, we suggest that negative molecular genetic findings in the proband and/or no clinical evidence of disease in their family members, integrated with the type of cardiomyopathy, may be helpful to estimate the family members' genetic risk. We emphasize that these risk assessments will vary greatly with the type of cardiomyopathy, because of the varied sensitivity of genetic testing (reviewed in the background to Recommendation 17.3). Thus, we have recommended longer intervals between clinical screenings with less evidence of disease, recognizing that lack of evidence may not necessarily be synonymous with lack of risk. We also acknowledge that while genetic testing is recommended, in some circumstances genetic testing cannot be performed because of a variety of issues (eg, deceased or unavailable proband, funding issues). Hence, the clinician must integrate all data − clinical and genetic − from the patient and his/her family members, to support the clinical decision analysis in genetic cardiomyopathy.

Integration of all of these considerations, most importantly the type of cardiomyopathy, should be taken into account in screening of children, as well, While children can manifest clinical cardiomyopathy, most disease is adolescent- (HCM) or adult-onset. Hence these recommendations should be integrated with the type of cardiomyopathy, the age of onset of other affected members in the pedigree when such data are available, the identity of the cardiomyopathy gene, and other features.

The testing modalities by diagnosis given in Recommendation 17.2 are screening tests to be performed during an initial evaluation of someone of unknown disease status. If any cardiovascular abnormalities are detected, additional testing specific for the cardiomyopathy should be obtained in order to secure a diagnosis and prognosis and to formulate an appropriate treatment plan.

The risks for developing HCM after 50 years of age are reduced but not eliminated[15] as are those for ARVD after 50 years of age.[16] The utility and role of Holter monitoring and the signal-averaged ECG in the diagnosis of ARVD has been reviewed.[16] Magnetic resonance imaging is useful for the diagnosis of ARVD in centers experienced in its use and interpretation for ARVD[17]; data are not yet available to guide the frequency of its application for screening at-risk family members.

The patient should be encouraged to communicate with at-risk relatives regarding the presenting symptoms of cardiomyopathy, regardless of whether clinical genetic testing is undertaken or, if undertaken, whether the results are positive or negative. They should be counseled to seek medical assistance with symptoms, and in particular be counseled that potentially imminently life-threatening symptoms, such as presyncope or syncope, should be brought to immediate medical attention.

Less evidence is available to support of the genetic basis of RCM than for the other cardiomyopathies, hence its reduced strength of evidence in these recommendations.

Recommendation

17.3 Evaluation, genetic counseling, and genetic testing of cardiomyopathy patients are complex processes. Referral to centers expert in genetic evaluation and family-based management should be considered. (Strength of Evidence = B)

Background

The processes involved in clinical and genetic evaluation and testing for cardiomyopathies, integrated with up-to-date genetic counseling, are complex. This is in part because these recommendations are rapidly evolving. Those practicing cardiovascular genetic medicine must remain up to date with the accelerating developments in the field, integrating clinical and genetic evaluations with genetic counseling. This includes knowledge of recent discoveries of mutations in genes not previously implicated in the cardiomyopathies, as well as emerging gene-phenotype and genotype-phenotype correlations. Complexity also results from the extensive locus (many genes) and allelic (many different mutations within those genes) heterogeneity. Advances in genetic testing technology are also leading to a proliferation of new genetic tests for the cardiomyopathies, which are all confounded by this locus and allelic heterogeneity.

This recommendation states that referral to centers expert in genetic evaluation and family-based management should be considered. ''Should be considered'' language was selected because the strength of the evidence varies

with the cardiomyopathy phenotype, the details of the clinical and family information, and other aspects of each situation. Some practitioners with experience in the field may be able to provide appropriate care for cardiomyopathy patients without referral to a geneticist or a cardiomyopathy center with expertise in genetics. In addition to clinical care for the patient's cardiomyopathy, the practitioner will need to select the indicated genetic tests, counsel the patient on the purpose and outcomes of the possible results prior to the collection of blood or other tissue for the test, and then interpret the results to the patient upon receiving test results.[18] Whether results are positive or negative, the practitioner also will need to counsel the patient on potential reproductive risks should the patient wish to have children. Referral to genetic counseling services should be considered if these genetic counseling activities exceed the practitioner's skill, interest, or available time.

Several diverse patient situations help clarify this recommendation. The first is that of a cardiomyopathy patient whose parents are deceased and has no siblings or offspring. The primary need for this patient is reproductive counseling; that is, counseling on the risks of transmitting his/her cardiomyopathy to offspring. As presented below, genetic testing is primarily indicated for risk assessment in at-risk relatives, and since this patient has no first-degree relatives, counseling for genetic testing would be directed to reproductive risk assessment.

A second case is that of a patient with restrictive cardiomyopathy with no obvious family history. Since the genetic testing indicated for restrictive cardiomyopathy is much less established than that for HCM or DCM, efforts should be directed to acquiring a complete and comprehensive 3−4 generation family history. While the practitioner needs to understand that the only known genetic basis of familial restrictive cardiomyopathy stems from genes associated with HCM, in most other respects obtaining the family history is similar to that of the other cardiomyopathies.[9] A skilled practitioner can accomplish this, but if obtaining a complete and comprehensive family history exceeds the skill, interest or available time, then referral should be considered.

In contrast to RCM, the genetic information, genetic testing and counseling available for HCM is extensive. The professional ordering genetic testing for HCM must be skilled in interpreting the genetic test results and the subsequent counseling based upon the integration of the results (positive or negative), the family history, the clinical data of the patient and any other known affected or unaffected family members. Ideally, the practitioner will also be skilled in the management of the clinical aspects of HCM, integrating the clinical, diagnostic and therapeutic recommendations based on a synthesis of all data.[14] This latter point is particularly relevant with HCM because of the complexity of decision analysis for clinical interventions (eg, the assessment of outflow tract obstruction, and if present, selection of a treatment plan that may involve surgical or catheter-based interventions). In most centers expert in providing care for genetic cardiomyopathies, cardiovascular clinicians knowledgeable and skilled in genetics rely on genetic counselors or geneticists to provide comprehensive services.[13,14,18] If executing and completing these aspects of management exceed the practitioner's skill, training, interest or available time, then referral to a cardiovascular center specializing in dealing with genetic cardiomyopathy should be considered.

A final example is the question of genetic testing for a familial dilated cardiomyopathy. Even though mutations in >20 genes have been implicated as causative in familial dilated cardiomyopathy (Table 17.2), the role of genetic testing for DCM at this time remains less certain because of the low test sensitivity. Testing recommendations in 17.4 are based in part on the frequency of mutations of certain genes (Table 17.2) and in part on certain phenotypic characteristics of DCM (eg, the almost universal conduction system disease observed in LMNA cardiomyopathy, discussed below). The field is rapidly evolving, and no one simple, comprehensive standard for risk assessment or genetic testing is presently applicable. Referral to a cardiovascular center specializing in genetic cardiomyopathy can assist in defining the appropriateness of genetic testing for DCM patients.

Practitioners may also consider referral to cardiovascular genetics centers to promote the engagement of patients in research. Patient involvement is critical for continued discovery of unknown genes that cause cardiomyopathy, for establishing long-term natural history studies, and for harnessing this information to improve diagnosis and to improve treatments.

The recommendation for genetic counseling for cardiomyopathy follows later (17.6).

Molecular Genetic Testing

Recommendation

17.4 Genetic testing should be considered for the one most clearly affected person in a family to facilitate family screening and management.

a. Cardiomyopathy phenotype

Cardiomyopathy Phenotype	Strength of Evidence
Hypertrophic cardiomyopathy (HCM)	A
Dilated cardiomyopathy (DCM)	B
Arrhythmic right ventricular dysplasia (ARVD)	A
Left ventricular noncompaction (LVNC)	C
Restrictive cardiomyopathy (RCM)	C
Cardiomyopathies associated with other extracardiac manifestataions	A

b. Specific genes available for screening based on cardiac phenotype

Cardiomyopathy Phenotype	Gene tests available*	Yield of positive results
HCM	MYH7, MYBPC3, TNNT2 TNNI3, TPMI, ACTC, MYL2, MYL3.	MYH7, MYBPC3 each account for 30−40% of mutations, TNNT2 for 10−20%. Genetic cause can be identified in 35−45% overall; up to 60−65% when the family history is positive.
DCM	LMNA, MYH7, TNNT2, SCN5A, DES, MYBPC3, TNNI3, TPMI, ACTC, PLN, LDB3 and TAZ.	5.5%, 4.2%, 2.9%, for LMNA, MYH7, and TNNT2, respectively. All data are from research cohorts.
ARVD	DSP, PKP2, DSG2, DSC2	6−16%, 11−43%, 12−40%, for DSP, PKP2 and DSG2, respectively
LVNC	Uncertain − see discussion	Uncertain − see discussion
RCM	Uncertain − see discussion	Uncertain − see discussion

*GeneTests (www.genetests.org) is an NIH funded resource that lists clinical (and research) molecular genetic testing laboratories for the cardiomyopathies.

c. Screening for Fabry disease is recommended in all men with sporadic or non-autosomal dominant (no male-to-male) transmission of unexplained cardiac hypertrophy. (Strength of Evidence = B)

Background

This recommendation is quite restrictive despite the extensive genetic information available. The rationale for the strength of evidence is derived largely from the published sensitivity of genetic testing, as presented in Tables 17.1-17.3. These recommendations do not address molecular testing in prenatal, newborn screening or in-vitro fertilization settings. Additional information for specific genes or genetic diagnoses are available at the Online Mendelian Inheritance in Man (OMIM) website (http://www.ncbi.nlm.nih.gov/sites/entrez?db=omim), which can be accessed using OMIM numbers assigned to genes (See Tables 17.1-17.3) or genetic condition (see Table 17.4) associated with cardiomyopathy.

Recommendation 17.4 states that the individual with the most evident disease should be the individual selected from a family to undergo genetic testing. This is a well established principle in clinical genetics, as selecting the individual with the most evident disease that has been clinically confirmed to a high degree of certainty decreases the probability of testing a phenocopy (someone who clinically has the disease from another cause and does not carry the family mutation) and thereby increases the likelihood of finding a genetic cause. Usually the individual

Table 17.3. Genetic causes of Arrhythmogenic Right Ventricular Dysplasia/Cardiomyopathy, Left Ventricular Noncompaction, and Restrictive Cardiomyopathy

Gene	Protein	OMIM	frequency*	Comments	Selected References
Arrrythmogenic Right Ventricular Dysplasia/Cardiomyopathy					
JUP	plakoglobin	173325	rare	Naxos disease, autosomal recessive	93−95
DSP	desmoplakin	125647	6−16%		1,96
PKP2	plakophilin-2	602861	11−43%		1,97,98
DSG2	desmoglein-2	125671	12−40%		1,99,100
DSC2	desmocollin-2	125645	rare		1,101,102
RYR2	ryanodine receptor	180902	rare		103
TGFB3	transforming growth factor beta-3	190230	rare		96,104
					105
Left Ventricular Noncompaction					
MYH7	β-myosin heavy chain	160760	?		106
LDB3	Limb domain binding protein 3	605906	?		80
DTNA	α-dystrobrevin	601239	?		107
TAZ	taffazzin	300394	?		107
Restrictive Cardiomyopathy					
MYH7	β-myosin heavy chain	160760	?		106,108
TNNI3	troponin I	191044	?		109

*frequency estimates for ARVD/C are from Genetests.

Table 17.4. Cardiomyopathies Associated with Systemic Disease

DCM
Duchenne Muscular Dystrophy
Becker Muscular Dystrophy
Emery-Dreifuss Muscular Dystrophy
Limb Girdle Muscular Dystrophy
Moyotonic Muscular Dystrophy
Mitochondrial Myopathy
Kearns-Sayre Syndrome
Myotubular (Centronuclear) Myopathy
Nemaline Myopathy
Cytochrome C Oxidase Deficiency
Barth Syndrome
Danon Disease
Fanconi Anemia
Diamond-Blackfan Syndrome
Sickle Cell Anemia
Medium Chain Acyl CoA Dehydrogenase Deficiency (MCAD)
Long Chain Acyl CoA Dehydrogenase Deficiency (LCAD)
Maroteaux-Lamy Syndrome
Fabry Disease
HCM
Fabry Disease
Friedreich's Ataxia
Noonan Syndrome
Costello Syndrome
LEOPARD Syndrome
Cardio-Facio-Cutaneous Syndrome
Hunter Syndrome
Hurler Syndrome
Hurler-Scheie Syndrome
Maroteaux-Lamy Syndrome
I-Cell Disease
Pompe Syndrome
Beckwith-Wiedemann Syndrome
Mitochondrial Myopathy
Cytochrome C Oxidase Deficiency
Barth Syndrome
Danon Disease
Down Syndrome
Proteus Syndrome
Yunis-Varon Syndrome
Pallister-Killian Mosaic Syndrome
Medium Chain Acyl CoA Dehydrogenase Deficiency (MCAD)
Long Chain Acyl CoA Dehydrogenase Deficiency (LCAD)
Multiple Sulfatase Deficiency
RCM
Amyloidosis
Sarcoidosis
Fabry Disease
Endomyocardial Fibrosis
Loffler's Eosinophilic Endomyocardial Disease
Pseudoxanthoma Elasticum
Desmin Myopathy
Gaucher Disease
LVNC
Mitochondrial Myopathy
Barth Syndrome
ARVD
Naxos Disease
Carvajal Syndrome

with more evident disease will also provide a more compelling phenotype, typically with more disease features, enabling the most accurate classification of the cardiomyopathy. Procurement of a tissue sample (preferentially tissue that has not been fixed) from an autopsy specimen can provide DNA for genetic testing. At times a DNA-containing sample from the family member with the most evident disease is not available, commonly because of death antecedent to the genetic analysis. Thus, another individual from the family must be selected for testing. Selection of a secondary individual for testing requires careful consideration, especially because of the low sensitivity for genetic testing for many cardiomyopathies. The professional selecting the individual for testing will need to consider the implications of negative genetic test results for that subject and have a plan for any additional testing for the remaining at-risk family members. On the other hand, if a mutation can be identified and the evidence supports its role as the disease-causing mutation, testing can be performed in relatives regardless of their clinical status.

Recommendation 17.4 also restricts the indication for genetic testing to that of *facilitation of family screening and management*. Simply put, this recognizes that currently the primary value, the primary reason to seek genetic testing for the genetic cardiomyopathies, is to more accurately predict the risk of a family member developing cardiomyopathy who currently has little or no clinical evidence of cardiovascular disease.

If a disease-causing mutation is identified in the affected family member initially tested, and subsequent genetic testing of an at-risk but presymptomatic family member is negative, that family member's risk of developing the cardiomyopathy is substantially reduced. In this situation the need for ongoing clinical screening in such a mutation-negative family member is not recommended. On the other hand, if a disease-causing mutation is identified in an asymptomatic, at-risk family member, the confidence is much greater to infer risk for that individual. The individual should be counseled on the presenting signs and symptoms of the specific cardiomyopathy, the associated reduced penetrance and variable expressivity, and the rationale and frequency of the recommended clinical surveillance.

Notably these recommendations are silent for any additional interventions specific for a disease-causing mutation. The reason for this stems from the lack of validated genotype-phenotype correlations of specific mutations with specific clinical cardiovascular outcomes. Unless or until specific mutations have been shown to reliably predict specific clinical outcomes (eg, increased or reduced risk of a specific event such as the development of symptomatic heart failure or the high probability of sudden cardiac death), the recommendations will refer to the general behavior of each disease gene.

The general characteristics of disease presentation and progression may suggest involvement of specific genes. We refer to this as 'gene-phenotype relationships' in contrast to the more commonly used 'genotype-phenotype relationships,' commonly used to indicate phenotypic characteristics of specific mutations. The strongest

evidence for gene-phenotype relationships is present for HCM and DCM (Table 17.5).

Recommendation 17.4, focused on genetic testing to facilitate family screening and management, is also silent for specific recommendations for apparent sporadic (non-familial) disease. However, considerable evidence suggests that HCM results from both sporadic and familial genetic disease.[11] In contrast, the etiology of DCM that does not appear to be familial remains enigmatic, as is the evidence to support an underlying genetic cause. Some patients with DCM, but without a positive family history, have been shown to harbor mutations consistent with genetic causation of their disease (Table 17.2). Further, the largest genetic survey to date of six DCM disease genes in 313 unrelated probands observed a similar frequency of mutations attributed to familial vs sporadic disease.[19] However, patient acquisition for that study was not specifically designed to address the frequency of the genetic basis of sporadic DCM versus familial disease, and familial disease was not excluded with prospective clinical screening of first-degree relatives in those assigned to have sporadic DCM. This is particularly relevant, as conducting clinical screening of first-degree family members with echocardiograpy and ECG has been shown to have four-fold greater sensitivity to detect familial DCM compared to obtaining a careful 3-generation family history.[20] Thus, a genetic etiology for the bulk of non-ischemic, presumably non-familial (sporadic) DCM, while plausible, is not yet supported by rigorous studies that provide robust, reliable estimates of the frequency of genetic causation.

HCM has the strongest evidence to support genetic testing (Table 17.1). ARVD/C, although quite rare, also has good evidence to support genetic testing (Table 17.3).

Testing for DCM is confounded by the question of etiology of sporadic DCM discussed above. It is also greatly confounded by the extensive genetic heterogeneity, as well as the relatively low frequency of involvement of any one gene in DCM. Technological advances will continue to improve testing methods, thereby dramatically decreasing costs. While such progress will make it possible to test many DCM genes simultaneously, it is likely that sequence variations of unknown significance will be discovered that may confound test interpretation.

However, testing for the *LMNA* gene is recommended in patients with prominent conduction disease with or without supraventricular or ventricular arrhythmias (Table 17.5), or with signs of skeletal muscle involvement, shown most commonly by elevated creatine kinase (CK-MM) because in both groups *LMNA* mutations appear to be at higher frequency (Table 17.5). *LMNA* molecular genetic testing may be considered for all DCM patients based on its overall higher frequency in DCM (Table 17.5: a mean of 7.3% of those with familial disease, or 3.0% of those with apparent sporadic disease, or 5.5% overall, as summarized from six studies [21–26]), and because of its diagnosis on prognosis and management.[27]

Data are only now emerging describing the genetic basis of LVNC, limiting strength of recommendations, as is the case for RCM (Table 17.3).

Clinical genetic testing should be carried out in a fully accredited molecular genetic testing laboratory that has met Clinical Laboratory Improvement Amendment (CLIA) standards. Clear distinctions should be made between testing for clinical purposes, as advocated by these recommendations, in CLIA-accredited laboratories and that undertaken for research purposes that cannot be used to direct clinical care (unless conducted in a CLIA-certified research laboratory that provides clinical reports). Because the genetic knowledge base of cardiomyopathy is still emerging, practitioners caring for patients and families with genetic cardiomyopathy are encouraged to consider research participation. Referral centers expert in genetic cardiomyopathy are experienced in explaining the roles and outcomes of clinical testing versus research participation, which may include research genetic testing, and are able to facilitate both objectives.[28]

Table 17.5. Cardiomyopathy Phenotypes Suggestive of Specific Disease Genes

Gene	Protein	Phenotype Summary*	Comments*	References
Dilated cardiomyopathy phenotype				
LMNA	lamin A/C	Prominent conduction system disease and arrhythmias, then DCM and heart failure	Asymptomatic ECG abnormalities, then sinus/AV node dysfunction; 1st, 2nd, 3rd degree heart block; Aflutter/Afib, tachy/brady syndrome, pacemakers common. Onset of DCM, with mild - severe LV dysfunction, then HF, SCD, advanced disease requiring cardiac transplantation	21–26,58–64
Hypertrophic cardiomyopathy phenotype				
MYH7	β-myosin heavy chain	wide age range; severe LVH; heart failure, SCD		10,11,37,38
MYBPC3	myosin-binding protein C	usually milder disease; some older onset		10,11,38,39
TNNT2	cardiac troponin T	mild LVH; SCD common		10,11,38,40

*Aflutter/Afib is atrial flutter and atrial fibrillation; AV is atrioventricular; SCD is sudden cardiac death; LVH is left ventricular hypertrophy.

Genetic Counseling

Recommendation

17.5 Genetic and family counseling is recommended for all patients and families with cardiomyopathy. (Strength of Evidence = A)

Background

Genetic counseling is the process of communicating relevant genetic information, including genetic risks, to patients and their families, so that they may understand the genetic information presented and use it to make informed decisions regarding genetic testing or other therapeutic decisions. The process also helps individuals to adapt to the medical, psychological and familial implications of genetic contributions to disease.[29] The majority of genetic counseling is performed by board-certified Master's level genetic counselors or by board-certified medical geneticists. Genetic counseling for the cardiomyopathies is best undertaken by genetic counselors, geneticists who are knowledgeable of the cardiovascular clinical features of the type of cardiomyopathy in question, or cardiologists who are expert in the cardiomyopathy in question and are fluent in the content and nature of genetic counseling for the patient and their family members.[13,18,30] Alliances of cardiologists with special interest and expertise in genetic cardiomyopathies with genetics professionals, usually Master's level trained genetic counselors or nurses trained in genetics, are beginning to emerge. In a survey of Dutch cardiologists and geneticists regarding the provision of care for HCM, most cardiologists preferred that pedigree construction, counseling and genetic testing be handled by geneticists, although a significant trend for collaborative arrangements between geneticists and cardiologists was also noted.[31]

Regardless of who provides it, genetic counseling is an essential component of the evaluation, diagnosis, and management of the cardiomyopathies.[13,18,30] Essential activities completed by a genetic counselor are obtaining a careful and comprehensive 3- to 4-generation family history; educating the patient and family regarding disease transmission and family risks; counseling regarding any genetic testing to be undertaken including the implications of positive, negative, or uncertain results; providing key information to other at-risk family members as identified by the index patient; and assisting with the interpretation of genetic test results and their integration into the overall treatment plan. Counseling is designed to promote informed choices and adaptation to the risk or condition by providing medical facts and options and social implications.

The first essential activity, obtaining a comprehensive family history, has already been was addressed earlier. The next objective is to educate the patient and family regarding the disease transmission and family risks. If genetic testing has identified a plausible genetic cause, counseling regarding transmission is conducted (autosomal or X-linked, either dominant or recessive). The pedigree is commonly utilized to inform the patient and family of at-risk members. If the patient presents without prior genetic testing, but testing is indicated, counseling is undertaken regarding the utility, sensitivity, analytic validity, and the implications of all possible testing outcomes based on the prior items. The patient, family members, or both need to be counseled on the possibility of identifying genetic variants of unknown significance. Counseling also involves exploring the psychosocial issues that are relevant to the condition or risk that the individual is facing, as well as addressing family dynamics, which could potentially impact dissemination of genetic information to at-risk family members.

Therapy Based on Genetic Testing

As already discussed, the finding of any specific mutation as the cause of the cardiomyopathy does not in itself guide therapy. However, the clinical characteristics associated with some disease genes (Table 17.5), when integrated with the clinical and family data, may influence the overall case assessment, and may appropriately impact all aspects of the clinical recommendations. This includes the frequency and stringency of presymptomatic screening for signs of disease, the strength of interventions to educate family members of risks and symptoms, the threshold for presymptomatic initiation of preventive (eg, ICDs in certain HCM, DCM or ARVD/C settings) or therapeutic interventions (eg, beta blockers or ACE inhibitors in presymptomatic DCM).

Therapy Based on Cardiac Phenotype

Recommendations

17.6 Medical therapy based on cardiac phenotype is recommended as outlined in the general guidelines. (Strength of Evidence = A)

17.7 Device therapies for arrhythmia and conduction system disease based on cardiac phenotype are recommended as outlined in the general guidelines. (Strength of Evidence = B)

17.8 In patients with cardiomyopathy and significant arrhythmia or known risk of arrhythmia an ICD may be considered before the left ventricular ejection fraction falls below 35%. (Strength of Evidence = C)

Background

Guidelines for clinical care of the patient with cardiomyopathies are available for HCM[32] and DCM (Sections 4−16, 34). These guidelines provide comprehensive guidance for care of those who are presymptomatic or have had the onset of clinical disease. Guidelines for the clinical care for ARVD, LVNC and RCM are not yet available.

In brief, implantable cardiac defibrillators (ICDs) are indicated for symptomatic or life-threatening arrhythmias

regardless of the type of cardiomyopathy diagnosis or ventricular function. The indications for ICDs are summarized for DCM in Section 9 and elsewhere.[33] For DCM, a left ventricular ejection less than 30-35% is usually an indication for an ICD, regardless of etiology.

Electrophysiological disease can be considered broadly as conduction system disease and arrhythmia. Conventional guidelines apply for symptomatic or pre-symptomatic conduction system disease regardless of other aspects of the patient's clinical situation.[34] Pacemakers are indicated for symptomatic bradycardia, high grade AV block regardless of symptoms, for any other symptomatic conduction system disease. In this setting of lamin A/C cardiomyopathy requiring pacemaker placement, the use of an ICD rather than a pacemaker has been recommended.[36] Such a course appears reasonable. Patients with a dilated cardiomyopathy but with EF $>$ 30−35% may be considered for an ICD if the family history is positive for SCD or for patients with LMNA mutations.[35]

Pediatric Forms of Inherited Cardiomyopathies

All phenotypes of cardiomyopathy presenting in childhood can occur as a genetic disorder. Unlike adult disease, pediatric cardiomyopathies, particularly those presenting in the first year of life, have an increased likelihood of being mitochondrial or metabolic-based. Evaluation of these young children must include studies aimed at determining whether mitochondrial dysfunction or metabolic derangement is central to the underlying basis of the cardiac disorder. In the case of mitochondrial disease, mitochondrial DNA (mtDNA) mutations inherited from the mother (maternal inheritance) or autosomal recessive inheritance underlie these disorders. Metabolic defects most commonly are inherited as autosomal recessive traits.

In the remaining cases of inherited cardiomyopathies of childhood, the same inheritance patterns as seen in adulthood are expected.

HCM of Childhood. Young children with left ventricular hypertrophy (LVH) may have an underlying mitochondrial or metabolic disease, while others have early clinical expression of HCM due to a sarcomere gene mutation. For instance, the deadly infiltrative lysosomal storage disorder, Pompe disease, or the benign infant of a diabetic mother form of LVH may appear to be similar by echocardiography. In addition, syndromes such as Noonan syndrome, overgrowth disorders such as Beckwith-Wiedeman syndrome or Sotos syndrome, or children with chromosomal disorders may present with LVH. A subgroup of these young children with LVH, however, has the typical ''adult form'' of disease caused by mutations in genes encoding sarcomere proteins.[36] Children can inherit these mutations or the gene defects can arise de novo and cause sporadic disease.

Children with HCM from mutations in sarcomeric genes typically demonstrate the classical clinical phenotypic features of HCM seen in adults. Phenotypic heterogeneity is common in children with familial forms of disease, both in clinical expression and outcome. For these reasons, the clinical follow-up of children with HCM tends to differ from that outlined for adults. Children younger than 1 year of age with HCM are usually seen frequently, commonly every 3 months. Siblings without clinical features of disease are followed yearly in most cases until reaching puberty. At that time, follow-up is every 1−2 years depending on their specific clinical, echocardiographic and electrocardiographic features. In cases where HCM presents in older children, the siblings are usually seen every 3 years unless a defect is identified.

DCM of Childhood. Inherited forms of DCM in childhood appear to exist in approximately 50% of affected subjects presenting by 18 years of age. Like HCM, mitochondrial and metabolic disease, as well as chromosomal defects and dysmorphic syndromes may be responsible for a substantial subgroup of cases. In the remaining inherited forms, autosomal and X-linked inheritance is most common. A substantial subgroup of children has associated skeletal myopathy, and some of these will also have conduction system disease. In inherited cases, similar to that described for HCM, onset of clinical features is age-dependent. In families with earlier onset of symptoms, follow-up of at-risk relatives should begin earlier. Relatives, particularly siblings, also follow a similar pattern as those outlined for relatives of HCM patients.

RCM of Childhood. Restrictive cardiomyopathy in childhood is an uncommon but serious form of cardiomyopathy. Inherited forms are infrequent, but when they occur appear to be associated with defective sarcomeric genes or mutations in desmin. Associated skeletal myopathy is common. In children with RCM, autosomal dominant inheritance predominates. Family evaluation for siblings tends to be approximately every 3 years unless a defect is identified.

LVNC of Childhood. Left ventricular noncompaction is seen during all ages of childhood from birth onward. Mitochondrial, metabolic, syndromic, chromosomal, and neuromuscular abnormalities are common. In addition, autosomal dominant inheritance is notable. LVNC is subdivided into dilated, hypertrophic, and hypertrophic/dilated forms, isolated LVNC without other abnormalities of size, thickness or function, and LVNC associated with congenital heart disease. Family members are followed every 3 years unless a defect is identified.

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