ACCF/AHA Practice Guideline

2013 ACCF/AHA Guideline for the Management of Heart Failure

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

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

Endorsed by the American Association of Cardiovascular and Pulmonary Rehabilitation

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Preamble

The medical profession should play a central role in evaluating the evidence related to drugs, devices, and procedures for the detection, management, and prevention of disease. When properly applied, expert analysis of available data on the benefits and risks of these therapies and procedures can improve the quality of care, optimize patient outcomes, and favorably affect costs by focusing resources on the most effective strategies. An organized and directed approach to a thorough review of evidence has resulted in the production of clinical practice guidelines that assist clinicians in selecting the best management strategy for an individual patient. Moreover, clinical practice guidelines can provide a foundation for other applications, such as performance measures, appropriate use criteria, and both quality improvement and clinical decision support tools.

The American College of Cardiology Foundation (ACCF) and the American Heart Association (AHA) have jointly produced guidelines in the area of cardiovascular disease since 1980. The ACCF/AHA Task Force on Practice Guidelines (Task Force), charged with developing, updating, and revising practice guidelines for cardiovascular diseases and procedures, directs and oversees this effort. Writing committees are charged with regularly reviewing and evaluating all available

Table 1. Applying Classification of Recommendation and Level of Evidence

ESTIMATE OF CERTAINTY (PRECISION) OF TREATMENT EFFECT	SIZE OF TREATMENT EFFECT: CLASS I *Benefit >>> Risk* Procedure/Treatment **SHOULD** be performed/ administered	CLASS IIa *Benefit >> Risk* *Additional studies with focused objectives needed* **IT IS REASONABLE** to perform procedure/administer treatment	CLASS IIb *Benefit ≥ Risk* *Additional studies with broad objectives needed; additional registry data would be helpful* Procedure/Treatment **MAY BE CONSIDERED**	CLASS III *No Benefit* or CLASS III *Harm* Procedure/ Test / Treatment COR III: No benefit / Not Helpful / No Proven Benefit COR III: Harm / Excess Cost w/o Benefit or Harmful / Harmful to Patients
LEVEL A Multiple populations evaluated* Data derived from multiple randomized clinical trials or meta-analyses	■ Recommendation that procedure or treatment is useful/effective ■ Sufficient evidence from multiple randomized trials or meta-analyses	■ Recommendation in favor of treatment or procedure being useful/effective ■ Some conflicting evidence from multiple randomized trials or meta-analyses	■ Recommendation's usefulness/efficacy less well established ■ Greater conflicting evidence from multiple randomized trials or meta-analyses	■ Recommendation that procedure or treatment is not useful/effective and may be harmful ■ Sufficient evidence from multiple randomized trials or meta-analyses
LEVEL B Limited populations evaluated* Data derived from a single randomized trial or nonrandomized studies	■ Recommendation that procedure or treatment is useful/effective ■ Evidence from single randomized trial or nonrandomized studies	■ Recommendation in favor of treatment or procedure being useful/effective ■ Some conflicting evidence from single randomized trial or nonrandomized studies	■ Recommendation's usefulness/efficacy less well established ■ Greater conflicting evidence from single randomized trial or nonrandomized studies	■ Recommendation that procedure or treatment is not useful/effective and may be harmful ■ Evidence from single randomized trial or nonrandomized studies
LEVEL C Very limited populations evaluated* Only consensus opinion of experts, case studies, or standard of care	■ Recommendation that procedure or treatment is useful/effective ■ Only expert opinion, case studies, or standard of care	■ Recommendation in favor of treatment or procedure being useful/effective ■ Only diverging expert opinion, case studies, or standard of care	■ Recommendation's usefulness/efficacy less well established ■ Only diverging expert opinion, case studies, or standard of care	■ Recommendation that procedure or treatment is not useful/effective and may be harmful ■ Only expert opinion, case studies, or standard of care
Suggested phrases for writing recommendations	should is recommended is indicated is useful/effective/beneficial	is reasonable can be useful/effective/beneficial is probably recommended or indicated	may/might be considered may/might be reasonable usefulness/effectiveness is unknown/unclear/uncertain or not well established	COR III: No Benefit: is not recommended; is not indicated; should not be performed/ administered/ other; is not useful/ beneficial/ effective COR III: Harm: potentially harmful; causes harm; associated with excess morbidity/mortality; should not be performed/ administered/ other
Comparative effectiveness phrases†	treatment/strategy A is recommended/indicated in preference to treatment B treatment A should be chosen over treatment B	treatment/strategy A is probably recommended/indicated in preference to treatment B it is reasonable to choose treatment A over treatment B		

A recommendation with Level of Evidence B or C does not imply that the recommendation is weak. Many important clinical questions addressed in the guidelines do not lend themselves to clinical trials. Although randomized trials are unavailable, there may be a very clear clinical consensus that a particular test or therapy is useful or effective.

*Data available from clinical trials or registries about the usefulness/efficacy in different subpopulations, such as sex, age, history of diabetes, history of prior myocardial infarction, history of heart failure, and prior aspirin use.

†For comparative effectiveness recommendations (Class I and IIa; Level of Evidence A and B only), studies that support the use of comparator verbs should involve direct comparisons of the treatments or strategies being evaluated.

evidence to develop balanced, patient-centric recommendations for clinical practice.

Experts in the subject under consideration are selected by the ACCF and AHA to examine subject-specific data and write guidelines in partnership with representatives from other medical organizations and specialty groups. Writing committees are asked to perform a literature review; weigh the strength of evidence for or against particular tests, treatments, or procedures; and include estimates of expected outcomes where such data exist. Patient-specific modifiers, comorbidities, and issues of patient preference that may influence the choice of tests or therapies are considered. When available, information from studies on cost is considered, but data on efficacy and outcomes constitute the primary basis for the recommendations contained herein.

In analyzing the data and developing recommendations and supporting text, the writing committee uses evidence-based methodologies developed by the Task Force.[1] The Class of Recommendation (COR) is an estimate of the size of the treatment effect considering risks versus benefits in addition to evidence and/or agreement that a given treatment or procedure is or is not useful/effective or in some situations may cause harm. The Level of Evidence (LOE) is an estimate of the certainty or precision of the treatment effect. The writing committee reviews and ranks evidence supporting each recommendation with the weight of evidence ranked as LOE A, B, or C according to specific definitions that are included in Table 1. Studies are identified as observational, retrospective, prospective, or randomized where appropriate. For certain conditions for which inadequate data are available, recommendations

are based on expert consensus and clinical experience and are ranked as LOE C. When recommendations at LOE C are supported by historical clinical data, appropriate references (including clinical reviews) are cited if available. For issues for which sparse data are available, a survey of current practice among the clinicians on the writing committee is the basis for LOE C recommendations and no references are cited. The schema for COR and LOE are summarized in Table 1, which also provides suggested phrases for writing recommendations within each COR. A new addition to this methodology is separation of the Class III recommendations to delineate whether the recommendation is determined to be of "no benefit" or is associated with "harm" to the patient. In addition, in view of the increasing number of comparative effectiveness studies, comparator verbs and suggested phrases for writing recommendations for the comparative effectiveness of one treatment or strategy versus another have been added for COR I and IIa, LOE A or B only.

In view of the advances in medical therapy across the spectrum of cardiovascular diseases, the Task Force has designated the term *guideline-directed medical therapy (GDMT)* to represent optimal medical therapy as defined by ACCF/AHA guideline–recommended therapies (primarily Class I). This new term, *GDMT*, will be used herein and throughout all future guidelines.

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

The ACCF/AHA practice guidelines are intended to assist clinicians in clinical decision making by describing a range of generally acceptable approaches to the diagnosis, management, and prevention of specific diseases or conditions. The guidelines attempt to define practices that meet the needs of most patients in most circumstances. The ultimate judgment regarding care of a particular patient must be made by the clinician and patient in light of all the circumstances presented by that patient. As a result, situations may arise for which deviations from these guidelines may be appropriate. Clinical decision making should involve consideration of the quality and availability of expertise in the area where care is provided. When these guidelines are used as the basis for regulatory or payer decisions, the goal should be improvement in quality of care. The Task Force recognizes that situations arise in which additional data are needed to inform patient care more effectively; these areas will be identified within each respective guideline when appropriate.

Prescribed courses of treatment in accordance with these recommendations are effective only if followed. Because lack of patient understanding and adherence may adversely affect outcomes, clinicians should make every effort to engage the patient's active participation in prescribed medical regimens and lifestyles. In addition, patients should be informed of the risks, benefits, and alternatives to a particular treatment and be involved in shared decision making whenever feasible, particularly for COR IIa and IIb, for which the benefit-to-risk ratio may be lower.

The Task Force makes every effort to avoid actual, potential, or perceived conflicts of interest that may arise as a result of industry relationships or personal interests among the members of the writing committee. All writing committee members and peer reviewers of the guideline are required to disclose all current healthcare-related relationships, including those existing 12 months before initiation of the writing effort. In December 2009, the ACCF and AHA implemented a new policy for relationship with industry and other entities (RWI) that requires the writing committee chair plus a minimum of 50% of the writing committee to have no *relevant* RWI (Appendix 1 includes the ACCF/AHA definition of relevance). These statements are reviewed by the Task Force and all members during each conference call and/or meeting of the writing committee and are updated as changes occur. All guideline recommendations require a confidential vote by the writing committee and must be approved by a consensus of the voting members. Members are not permitted to draft or vote on any text or recommendations pertaining to their RWI. Members who recused themselves from voting are indicated in the list of writing committee members, and specific section recusals are noted in Appendix 1. Authors' and peer reviewers' RWI pertinent to this guideline are disclosed in Appendixes 1 and 2, respectively. Additionally, to ensure complete transparency, writing committee members' comprehensive disclosure information—including RWI not pertinent to this document—is available as an online supplement. Comprehensive disclosure information for the Task Force is also available online at http://www.cardiosource.org/en/ACC/About-ACC/Who-We-Are/Leadership/Guidelines-and-Documents-Task-Forces.aspx. The work of writing committees is supported exclusively by the ACCF and AHA without commercial support. Writing committee members volunteered their time for this activity.

In an effort to maintain relevance at the point of care for practicing clinicians, the Task Force continues to oversee an ongoing process improvement initiative. As a result, in response to pilot projects, several changes to these guidelines will be apparent, including limited narrative text, a focus on summary and evidence tables (with references linked to abstracts in PubMed), and more liberal use of summary recommendation tables (with references that support LOE) to serve as a quick reference.

In April 2011, the Institute of Medicine released 2 reports: *Clinical Practice Guidelines We Can Trust* and *Finding What Works in Health Care: Standards for Systematic Reviews.*[2,3] It is noteworthy that the ACCF/AHA practice guidelines are cited as being compliant with many of the proposed standards. A thorough review of these reports and of our current methodology is under way, with further enhancements anticipated.

The recommendations in this guideline are considered current until they are superseded by a focused update or the full-text guideline is revised. Guidelines are official policy of both the ACCF and AHA.

Jeffrey L. Anderson, MD, FACC, FAHA
Chair, ACCF/AHA Task Force on Practice Guidelines

1. Introduction

1.1. Methodology and Evidence Review

The recommendations listed in this document are, whenever possible, evidence based. An extensive evidence review was conducted through October 2011 and includes selected other references through April 2013. Searches were extended to studies, reviews, and other evidence conducted in human subjects and that were published in English from PubMed, EMBASE, Cochrane, Agency for Healthcare Research and Quality Reports, and other selected databases relevant to this guideline. Key search words included but were not limited to the following: *heart failure, cardiomyopathy, quality of life, mortality, hospitalizations, prevention, biomarkers, hypertension, dyslipidemia, imaging, cardiac catheterization, endomyocardial biopsy, angiotensin-converting enzyme inhibitors, angiotensin-receptor antagonists/blockers, beta blockers, cardiac, cardiac resynchronization therapy, defibrillator*, *device-based therapy, implantable cardioverter-defibrillator, device implantation, medical therapy, acute decompensated heart failure, preserved ejection fraction, terminal care and transplantation, quality measures,* and *performance measures*. Additionally, the committee reviewed documents related to the subject matter previously published by the ACCF and AHA. References selected and published in this document are representative and not all-inclusive.

To provide clinicians with a representative evidence base, whenever deemed appropriate or when published, the absolute risk difference and number needed to treat or harm are provided in the guideline (within tables), along with confidence intervals and data related to the relative treatment effects such as odds ratio, relative risk, hazard ratio, and incidence rate ratio.

1.2. Organization of the Writing Committee

The committee was composed of physicians and a nurse with broad expertise in the evaluation, care, and management of patients with heart failure (HF). The authors included general cardiologists, HF and transplant specialists, electrophysiologists, general internists, and physicians with methodological expertise. The committee included representatives from the ACCF, AHA, American Academy of Family Physicians, American College of Chest Physicians, American College of Physicians, Heart Rhythm Society, and International Society for Heart and Lung Transplantation.

1.3. Document Review and Approval

This document was reviewed by 2 official reviewers each nominated by both the ACCF and the AHA, as well as 1 to 2 reviewers each from the American Academy of Family Physicians, American College of Chest Physicians, Heart Rhythm Society, and International Society for Heart and Lung Transplantation, as well as 32 individual content reviewers (including members of the ACCF Adult Congenital and Pediatric Cardiology Council, ACCF Cardiovascular Team Council, ACCF Council on Cardiovascular Care for Older Adults, ACCF Electrophysiology Committee, ACCF Heart Failure and Transplant Council, ACCF Imaging Council, ACCF Prevention Committee, ACCF Surgeons' Scientific Council, and ACCF Task Force on Appropriate Use Criteria). All information on reviewers' RWI was distributed to the writing committee and is published in this document (Appendix 2).

This document was approved for publication by the governing bodies of the ACCF and AHA and endorsed by the American Association of Cardiovascular and Pulmonary Rehabilitation, American College of Chest Physicians, Heart Rhythm Society, and International Society for Heart and Lung Transplantation.

1.4. Scope of This Guideline With Reference to Other Relevant Guidelines or Statements

This guideline covers multiple management issues for the adult patient with HF. Although there is an abundance of evidence addressing HF, for many important clinical considerations, this writing committee was unable to identify sufficient data to properly inform a recommendation. The writing committee actively worked to reduce the number of LOE "C" recommendations, especially for Class I–recommended therapies. Despite these limitations, it is apparent that much can be done for HF. Adherence to the clinical practice guidelines herein reproduced should lead to improved patient outcomes.

Although of increasing importance, HF in children and congenital heart lesions in adults are not specifically addressed in this guideline. The reader is referred to publically available resources to address questions in these areas. However, this guideline does address HF with preserved ejection fraction (EF) in more detail and similarly revisits hospitalized HF. Additional areas of renewed interest are in stage D HF, palliative care, transition of care, and quality of care for HF. Certain management strategies appropriate for the patient at risk for HF or already affected by HF are also reviewed in numerous relevant clinical practice guidelines and scientific statements published by the ACCF/AHA Task Force on Practice Guidelines, AHA, ACCF Task Force on Appropriate Use Criteria, European Society of Cardiology, Heart Failure Society of America, and the National Heart, Lung, and Blood Institute. The writing committee saw no need to reiterate the recommendations contained in those guidelines and chose to harmonize recommendations when appropriate and eliminate discrepancies. This is especially the case for device-based therapeutics, where complete alignment between the HF guideline and the device-based therapy guideline was deemed imperative.[4] Some recommendations from earlier guidelines have been updated as warranted by new evidence or a better understanding of earlier evidence, whereas others that were no longer accurate or relevant or which were overlapping were modified; recommendations from previous guidelines that were similar or redundant were eliminated or consolidated when possible.

The present document recommends a combination of lifestyle modifications and medications that constitute GDMT. GDMT is specifically referenced in the recommendations for the treatment of HF (Section 7.3.2). Both for GDMT and other recommended drug treatment regimens, the reader is advised to confirm dosages with product insert material and to evaluate carefully for contraindications and drug-drug interactions. Table 2 is a list of documents deemed pertinent to this effort and is intended for use as a resource; it obviates the need to repeat already extant guideline recommendations. Additional other HF guideline statements are highlighted as well for the purpose of comparison and completeness.

Table 2. Associated Guidelines and Statements

Title	Organization	Publication Year (Reference)
Guidelines		
Guidelines for the Management of Adults With Congenital Heart Disease	ACCF/AHA	2008[5]
Guidelines for the Management of Patients With Atrial Fibrillation	ACCF/AHA/HRS	2011[6–8]
Guideline for Assessment of Cardiovascular Risk in Asymptomatic Adults	ACCF/AHA	2010[9]
Guideline for Coronary Artery Bypass Graft Surgery	ACCF/AHA	2011[10]
Guidelines for Device-Based Therapy of Cardiac Rhythm Abnormalities	ACCF/AHA/HRS	2013[4]
Guideline for the Diagnosis and Treatment of Hypertrophic Cardiomyopathy	ACCF/AHA	2011[11]
Guideline for Percutaneous Coronary Intervention	ACCF/AHA/SCAI	2011[12]
Secondary Prevention and Risk Reduction Therapy for Patients With Coronary and Other Atherosclerotic Vascular Disease: 2011 Update	AHA/ACCF	2011[13]
Guideline for the Diagnosis and Management of Patients With Stable Ischemic Heart Disease	ACCF/AHA/ACP/AATS/PCNA/SCAI/STS	2012[14]
Guideline for the Management of ST-Elevation Myocardial Infarction	ACCF/AHA	2013[15]
Guidelines for the Management of Patients With Unstable Angina/Non–ST-Elevation Myocardial Infarction	ACCF/AHA	2013[16]
Guidelines for the Management of Patients With Valvular Heart Disease	ACCF/AHA	2008[17]
Comprehensive Heart Failure Practice Guideline	HFSA	2010[18]
Guidelines for the Diagnosis and Treatment of Acute and Chronic Heart Failure	ESC	2012[19]
Chronic Heart Failure: Management of Chronic Heart Failure in Adults in Primary and Secondary Care	NICE	2010[20]
Antithrombotic Therapy and Prevention of Thrombosis	ACCP	2012[21]
Guidelines for the Care of Heart Transplant Recipients	ISHLT	2010[22]
Statements		
Contemporary Definitions and Classification of the Cardiomyopathies	AHA	2006[23]
Genetics and Cardiovascular Disease	AHA	2012[24]
Appropriate Utilization of Cardiovascular Imaging in Heart Failure	ACCF	2013[25]
Appropriate Use Criteria for Coronary Revascularization Focused Update	ACCF	2012[26]
Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure	NHLBI	2003[27]
Implications of Recent Clinical Trials for the National Cholesterol Education Program Adult Treatment Panel III Guidelines	NHLBI	2002[28]
Referral, Enrollment, and Delivery of Cardiac Rehabilitation/Secondary Prevention Programs at Clinical Centers and Beyond	AHA/AACVPR	2011[29]
Decision Making in Advanced Heart Failure	AHA	2012[30]
Recommendations for the Use of Mechanical Circulatory Support: Device Strategies and Patient Selection	AHA	2012[31]
Advanced Chronic Heart Failure	ESC	2007[32]
Oral Antithrombotic Agents for the Prevention of Stroke in Nonvalvular Atrial Fibrillation	AHA/ASA	2012[33]
Third Universal Definition of Myocardial Infarction	ESC/ACCF/AHA/WHF	2012[34]

AACVPR indicates American Association of Cardiovascular and Pulmonary Rehabilitation; AATS, American Association for Thoracic Surgery; ACCF, American College of Cardiology Foundation; ACCP, American College of Chest Physicians; ACP, American College of Physicians; AHA, American Heart Association; ASA, American Stroke Association; ESC, European Society of Cardiology; HFSA, Heart Failure Society of America; HRS, Heart Rhythm Society; ISHLT, International Society for Heart and Lung Transplantation; NHLBI, National Heart, Lung, and Blood Institute; NICE, National Institute for Health and Clinical Excellence; PCNA, Preventive Cardiovascular Nurses Association; SCAI, Society for Cardiovascular Angiography and Interventions; STS, Society of Thoracic Surgeons; and WHF, World Heart Federation.

2. Definition of HF

HF is a complex clinical syndrome that results from any structural or functional impairment of ventricular filling or ejection of blood. The cardinal manifestations of HF are dyspnea and fatigue, which may limit exercise tolerance, and fluid retention, which may lead to pulmonary and/or splanchnic congestion and/or peripheral edema. Some patients have exercise intolerance but little evidence of fluid retention, whereas others complain primarily of edema, dyspnea, or fatigue. Because some patients present without signs or symptoms of volume overload, the term "heart failure" is preferred over "congestive heart failure." There is no single diagnostic test for HF because it is largely a clinical diagnosis based on a careful history and physical examination.

The clinical syndrome of HF may result from disorders of the pericardium, myocardium, endocardium, heart valves, or great vessels or from certain metabolic abnormalities, but most patients with HF have symptoms due to impaired left ventricular (LV) myocardial function. It should be emphasized

Table 3. Definitions of HF*r*EF and HF*p*EF

Classification	EF (%)	Description
I. Heart failure with reduced ejection fraction (HF*r*EF)	≤40	Also referred to as systolic HF. Randomized controlled trials have mainly enrolled patients with HF*r*EF, and it is only in these patients that efficacious therapies have been demonstrated to date.
II. Heart failure with preserved ejection fraction (HF*p*EF)	≥50	Also referred to as diastolic HF. Several different criteria have been used to further define HF*p*EF. The diagnosis of HF*p*EF is challenging because it is largely one of excluding other potential noncardiac causes of symptoms suggestive of HF. To date, efficacious therapies have not been identified.
a. HF*p*EF, borderline	41 to 49	These patients fall into a borderline or intermediate group. Their characteristics, treatment patterns, and outcomes appear similar to those of patients with HF*p*EF.
b. HF*p*EF, improved	>40	It has been recognized that a subset of patients with HF*p*EF previously had HF*r*EF. These patients with improvement or recovery in EF may be clinically distinct from those with persistently preserved or reduced EF. Further research is needed to better characterize these patients.

EF indicates ejection fraction; HF, heart failure; HF*p*EF, heart failure with preserved ejection fraction; and HF*r*EF, heart failure with reduced ejection fraction.

that HF is not synonymous with either cardiomyopathy or LV dysfunction; these latter terms describe possible structural or functional reasons for the development of HF. HF may be associated with a wide spectrum of LV functional abnormalities, which may range from patients with normal LV size and preserved EF to those with severe dilatation and/or markedly reduced EF. In most patients, abnormalities of systolic and diastolic dysfunction coexist, irrespective of EF. EF is considered important in classification of patients with HF because of differing patient demographics, comorbid conditions, prognosis, and response to therapies[35] and because most clinical trials selected patients based on EF. EF values are dependent on the imaging technique used, method of analysis, and operator. Because other techniques may indicate abnormalities in systolic function among patients with a preserved EF, it is preferable to use the terms preserved or reduced EF over preserved or reduced systolic function. For the remainder of this guideline, we will consistently refer to HF with preserved EF and HF with reduced EF as HF*p*EF and HF*r*EF, respectively (Table 3).

2.1. HF With Reduced EF (HF*r*EF)

In approximately half of patients with HF*r*EF, variable degrees of LV enlargement may accompany HF*r*EF.[36,37] The definition of HF*r*EF has varied, with guidelines of left ventricular ejection fraction (LVEF) ≤35%, <40%, and ≤40%.[18,19,38] Randomized controlled trials (RCTs) in patients with HF have mainly enrolled patients with HF*r*EF with an EF ≤35% or ≤40%, and it is only in these patients that efficacious therapies have been demonstrated to date. For the present guideline, HF*r*EF is defined as the clinical diagnosis of HF and EF ≤40%. Those with LV systolic dysfunction commonly have elements of diastolic dysfunction as well.[39] Although coronary artery disease (CAD) with antecedent myocardial infarction (MI) is a major cause of HF*r*EF, many other risk factors (Section 4.6) may lead to LV enlargement and HF*r*EF.

2.2. HF With Preserved EF (HF*p*EF)

In patients with clinical HF, studies estimate that the prevalence of HF*p*EF is approximately 50% (range 40% to 71%).[40] These estimates vary largely because of the differing EF cutoff criteria and challenges in diagnostic criteria for HF*p*EF. HF*p*EF has been variably classified as EF >40%, >45%, >50%, and ≥55%. Because some of these patients do not have entirely normal EF but also do not have major reduction in systolic function, the term *preserved EF* has been used. Patients with an EF in the range of 40% to 50% represent an intermediate group. These patients are often treated for underlying risk factors and comorbidities and with GDMT similar to that used in patients with HF*r*EF. Several criteria have been proposed to define the syndrome of HF*p*EF. These include a) clinical signs or symptoms of HF; b) evidence of preserved or normal LVEF; and c) evidence of abnormal LV diastolic dysfunction that can be determined by Doppler echocardiography or cardiac catheterization.[41] The diagnosis of HF*p*EF is more challenging than the diagnosis of HF*r*EF because it is largely one of excluding other potential noncardiac causes of symptoms suggestive of HF. Studies have suggested that the incidence of HF*p*EF is increasing and that a greater portion of patients hospitalized with HF have HF*p*EF.[42] In the general population, patients with HF*p*EF are usually older women with a history of hypertension. Obesity, CAD, diabetes mellitus, atrial fibrillation (AF), and hyperlipidemia are also highly prevalent in HF*p*EF in population-based studies and registries.[40,43] Despite these associated cardiovascular risk factors, hypertension remains the most important cause of HF*p*EF, with a prevalence of 60% to 89% from large controlled trials, epidemiological studies, and HF registries.[44] It has been recognized that a subset of patients with HF*p*EF previously had HF*r*EF.[45] These patients with improvement or recovery in EF may be clinically distinct from those with persistently preserved or reduced EF. Further research is needed to better characterize these patients.

See Online Data Supplement 1 for additional data on HFpEF.

3. HF Classifications

Both the ACCF/AHA stages of HF[38] and the New York Heart Association (NYHA) functional classification[38,46] provide useful and complementary information about the presence and severity of HF. The ACCF/AHA stages of HF emphasize the development and progression of disease and can be used to describe individuals and populations, whereas the NYHA classes focus on exercise capacity and the symptomatic status of the disease (Table 4).

Table 4. Comparison of ACCF/AHA Stages of HF and NYHA Functional Classifications

ACCF/AHA Stages of HF[38]		NYHA Functional Classification[46]	
A	At high risk for HF but without structural heart disease or symptoms of HF	None	
B	Structural heart disease but without signs or symptoms of HF	I	No limitation of physical activity. Ordinary physical activity does not cause symptoms of HF.
C	Structural heart disease with prior or current symptoms of HF	I	No limitation of physical activity. Ordinary physical activity does not cause symptoms of HF.
		II	Slight limitation of physical activity. Comfortable at rest, but ordinary physical activity results in symptoms of HF.
		III	Marked limitation of physical activity. Comfortable at rest, but less than ordinary activity causes symptoms of HF.
		IV	Unable to carry on any physical activity without symptoms of HF, or symptoms of HF at rest.
D	Refractory HF requiring specialized interventions	IV	Unable to carry on any physical activity without symptoms of HF, or symptoms of HF at rest.

ACCF indicates American College of Cardiology Foundation; AHA, American Heart Association; HF, heart failure; and NYHA, New York Heart Association.

The ACCF/AHA stages of HF recognize that both risk factors and abnormalities of cardiac structure are associated with HF. The stages are progressive and inviolate; once a patient moves to a higher stage, regression to an earlier stage of HF is not observed. Progression in HF stages is associated with reduced 5-year survival and increased plasma natriuretic peptide concentrations.[47] Therapeutic interventions in each stage aimed at modifying risk factors (stage A), treating structural heart disease (stage B), and reducing morbidity and mortality (stages C and D) (covered in detail in Section 7) are reviewed in this document. The NYHA functional classification gauges the severity of symptoms in those with structural heart disease, primarily stages C and D. It is a subjective assessment by a clinician and can change frequently over short periods of time. Although reproducibility and validity may be problematic,[48] the NYHA functional classification is an independent predictor of mortality.[49] It is widely used in clinical practice and research and for determining the eligibility of patients for certain healthcare services.

See Online Data Supplement 2 for additional data on ACCF/AHA stages of HF and NYHA functional classifications.

4. Epidemiology

The lifetime risk of developing HF is 20% for Americans ≥40 years of age.[50] In the United States, HF incidence has largely remained stable over the past several decades, with >650 000 new HF cases diagnosed annually.[51–53] HF incidence increases with age, rising from approximately 20 per 1000 individuals 65 to 69 years of age to >80 per 1000 individuals among those ≥85 years of age.[52] Approximately 5.1 million persons in the United States have clinically manifest HF, and the prevalence continues to rise.[51] In the Medicare-eligible population, HF prevalence increased from 90 to 121 per 1000 beneficiaries from 1994 to 2003.[52] HF*r*EF and HF*p*EF each make up about half of the overall HF burden.[54] One in 5 Americans will be >65 years of age by 2050.[55] Because HF prevalence is highest in this group, the number of Americans with HF is expected to significantly worsen in the future. Disparities in the epidemiology of HF have been identified. Blacks have the highest risk for HF.[56] In the ARIC (Atherosclerosis Risk in Communities) study, incidence rate per 1000 person-years was lowest among white women[52,53] and highest among black men,[57] with blacks having a greater 5-year mortality rate than whites.[58] HF in non-Hispanic black males and females has a prevalence of 4.5% and 3.8%, respectively, versus 2.7% and 1.8% in non-Hispanic white males and females, respectively.[51]

4.1. Mortality

Although survival has improved, the absolute mortality rates for HF remain approximately 50% within 5 years of diagnosis.[53,59] In the ARIC study, the 30-day, 1-year, and 5-year case fatality rates after hospitalization for HF were 10.4%, 22%, and 42.3%, respectively.[58] In another population cohort study with 5-year mortality data, survival for stage A, B, C, and D HF was 97%, 96%, 75%, and 20%, respectively.[47] Thirty-day postadmission mortality rates decreased from 12.6% to 10.8% from 1993 to 2005; however, this was due to lower in-hospital death rates. Postdischarge mortality actually increased from 4.3% to 6.4% during the same time frame.[60] These observed temporal trends in HF survival are primarily restricted to patients with reduced EF and are not seen in those with preserved EF.[40]

See Online Data Supplement 3 for additional data on mortality.

4.2. Hospitalizations

HF is the primary diagnosis in >1 million hospitalizations annually.[51] Patients hospitalized for HF are at high risk for all-cause rehospitalization, with a 1-month readmission rate of 25%.[61] In 2013, physician office visits for HF cost $1.8 billion. The total cost of HF care in the United States exceeds $30 billion annually, with over half of these costs spent on hospitalizations.[51]

4.3. Asymptomatic LV Dysfunction

The prevalence of asymptomatic LV systolic or diastolic dysfunction ranges from 6% to 21% and increases with age.[62–64] In the Left Ventricular Dysfunction Prevention study, participants with untreated asymptomatic LV dysfunction had a 10% risk for developing HF symptoms and an 8% risk of death or HF hospitalization annually.[65] In a community-based population, asymptomatic mild LV diastolic dysfunction was seen in 21% and moderate or severe diastolic dysfunction in 7%, and both were associated with an increased risk of symptomatic HF and mortality.[64]

4.4. Health-Related Quality of Life and Functional Status

HF significantly decreases health-related quality of life (HRQOL), especially in the areas of physical functioning and vitality.[66,67] Lack of improvement in HRQOL after discharge from the hospital is a powerful predictor of rehospitalization and mortality.[68,69] Women with HF have consistently been found to have poorer HRQOL than men.[67,70] Ethnic differences also have been found, with Mexican Hispanics reporting better HRQOL than other ethnic groups in the United States.[71] Other determinants of poor HRQOL include depression, younger age, higher body mass index (BMI), greater symptom burden, lower systolic blood pressure, sleep apnea, low perceived control, and uncertainty about prognosis.[70,72–76] Memory problems may also contribute to poor HRQOL.[76]

Pharmacological therapy is not a consistent determinant of HRQOL; therapies such as angiotensin-converting enzyme (ACE) inhibitors and angiotensin-receptor blockers (ARBs) improve HRQOL only modestly or delay the progressive worsening of HRQOL in HF.[77] At present, the only therapies shown to improve HRQOL are cardiac resynchronization therapy (CRT)[78] and certain disease management and educational approaches.[79–82] Self-care and exercise may improve HRQOL, but the results of studies evaluating these interventions are mixed.[83–86] Throughout this guideline we refer to meaningful survival as a state in which HRQOL is satisfactory to the patient.

See Online Data Supplement 4 for additional data on HRQOL and functional capacity.

4.5. Economic Burden of HF

In 1 in 9 deaths in the United States, HF is mentioned on the death certificate. The number of deaths with any mention of HF was as high in 2006 as it was in 1995.[51] Approximately 7% of all cardiovascular deaths are due to HF.

As previously noted, in 2013, HF costs in the United States exceeded $30 billion.[51] This total includes the cost of healthcare services, medications, and lost productivity. The mean cost of HF-related hospitalizations was $23 077 per patient and was higher when HF was a secondary rather than the primary diagnosis. Among patients with HF in 1 large population study, hospitalizations were common after HF diagnosis, with 83% of patients hospitalized at least once and 43% hospitalized at least 4 times. More than half of the hospitalizations were related to noncardiovascular causes.[87–89]

4.6. Important Risk Factors for HF (Hypertension, Diabetes Mellitus, Metabolic Syndrome, and Atherosclerotic Disease)

Many conditions or comorbidities are associated with an increased propensity for structural heart disease. The expedient identification and treatment of these comorbid conditions may forestall the onset of HF.[14,27,90] A list of the important documents that codify treatment for these concomitant conditions appears in Table 2.

Hypertension

Hypertension may be the single most important modifiable risk factor for HF in the United States. Hypertensive men and women have a substantially greater risk for developing HF than normotensive men and women.[91] Elevated levels of diastolic and especially systolic blood pressure are major risk factors for the development of HF.[91,92] The incidence of HF is greater with higher levels of blood pressure, older age, and longer duration of hypertension. Long-term treatment of both systolic and diastolic hypertension reduces the risk of HF by approximately 50%.[93–96] With nearly a quarter of the American population afflicted by hypertension and the lifetime risk of developing hypertension at >75% in the United States,[97] strategies to control hypertension are a vital part of any public health effort to prevent HF.

Diabetes Mellitus

Obesity and insulin resistance are important risk factors for the development of HF.[98,99] The presence of clinical diabetes mellitus markedly increases the likelihood of developing HF in patients without structural heart disease[100] and adversely affects the outcomes of patients with established HF.[101,102]

Metabolic Syndrome

The metabolic syndrome includes any 3 of the following: abdominal adiposity, hypertriglyceridemia, low high-density lipoprotein, hypertension, and fasting hyperglycemia. The prevalence of metabolic syndrome in the United States exceeds 20% of persons ≥20 years of age and 40% of those >40 years of age.[103] The appropriate treatment of hypertension, diabetes mellitus, and dyslipidemia[104] can significantly reduce the development of HF.

Atherosclerotic Disease

Patients with known atherosclerotic disease (eg, of the coronary, cerebral, or peripheral blood vessels) are likely to develop HF, and clinicians should seek to control vascular risk factors in such patients according to guidelines.[13]

5. Cardiac Structural Abnormalities and Other Causes of HF

5.1. Dilated Cardiomyopathies

5.1.1. Definition and Classification of Dilated Cardiomyopathies

Dilated cardiomyopathy (DCM) refers to a large group of heterogeneous myocardial disorders that are characterized by ventricular dilation and depressed myocardial contractility in the absence of abnormal loading conditions such as hypertension or valvular disease. In clinical practice and multicenter HF trials, the etiology of HF has often been categorized into ischemic or nonischemic cardiomyopathy, with the term DCM used interchangeably with nonischemic cardiomyopathy. This approach fails to recognize that "nonischemic cardiomyopathy" may include cardiomyopathies due to volume or pressure overload, such as hypertension or valvular heart disease, which are not conventionally accepted as DCM.[105] With the identification of genetic defects in several forms of cardiomyopathies, a new classification scheme based on genomics was proposed in 2006.[23] We recognize that classification of cardiomyopathies is challenging, mixing anatomic designations (ie, hypertrophic and dilated) with functional designations (ie, restrictive), and is unlikely to satisfy all users. The aim of the

present guideline is to target appropriate diagnostic and treatment strategies for preventing the development and progression of HF in patients with cardiomyopathies; we do not wish to redefine new classification strategies for cardiomyopathies.

5.1.2. Epidemiology and Natural History of DCM

The age-adjusted prevalence of DCM in the United States averages 36 cases per 100 000 population, and DCM accounts for 10 000 deaths annually.[106] In most multicenter RCTs and registries in HF, approximately 30% to 40% of enrolled patients have DCM.[107–109] Compared with whites, African Americans have almost a 3-fold increased risk for developing DCM, irrespective of comorbidities or socioeconomic factors.[108–110] Sex-related differences in the incidence and prognosis of DCM are conflicting and may be confounded by differing etiologies.[108,109,111] The prognosis in patients with symptomatic HF and DCM is relatively poor, with 25% mortality at 1 year and 50% mortality at 5 years.[112] Approximately 25% of patients with DCM with recent onset of HF symptoms will improve within a short time even in the absence of optimal GDMT,[113] but patients with symptoms lasting >3 months who present with severe clinical decompensation generally have less chance of recovery.[113] Patients with idiopathic DCM have a lower total mortality rate than patients with other types of DCM.[114] However, GDMT is beneficial in all forms of DCM.[78,109,115–117]

5.2. Familial Cardiomyopathies

Increasingly, it is recognized that many (20% to 35%) patients with an idiopathic DCM have a familial cardiomyopathy (defined as 2 closely related family members who meet the criteria for idiopathic DCM).[118,119] Consideration of familial cardiomyopathies includes the increasingly important discovery of noncompaction cardiomyopathies. Advances in technology permitting high-throughput sequencing and genotyping at reduced costs have brought genetic screening to the clinical arena. For further information on this topic, the reader is referred to published guidelines, position statements, and expert consensus statements[118,120–123] (Table 5).

5.3. Endocrine and Metabolic Causes of Cardiomyopathy

5.3.1. Obesity

Obesity cardiomyopathy is defined as cardiomyopathy due entirely or predominantly to obesity (Section 7.3.1.5). Although the precise mechanisms causing obesity-related HF are not known, excessive adipose accumulation results in an increase in circulating blood volume. A subsequent, persistent increase in cardiac output, cardiac work, and systemic blood pressure[124] along with lipotoxicity-induced cardiac myocyte injury and myocardial lipid accumulation have been implicated as potential mechanisms.[125,126]A study with participants from the Framingham Heart Study reported that after adjustment for established risk factors, obesity was associated with significant future risk of development of HF.[99] There are no large-scale studies of the safety or efficacy of weight loss with diet, exercise, or bariatric surgery in obese patients with HF.

5.3.2. Diabetic Cardiomyopathy

Diabetes mellitus is now well recognized as a risk factor for the development of HF independent of age, hypertension, obesity, hypercholesterolemia, or CAD. The association between mortality and hemoglobin A1c (HbA1c) in patients with diabetes mellitus and HF appears U-shaped, with the lowest risk of death in those patients with modest glucose control ($7.1\% < \text{HbA1c} \leq 7.8\%$) and with increased risk with extremely high or low HbA1c levels.[127] The optimal treatment strategy in patients with diabetes mellitus and HF is controversial; some studies have suggested potential harm with several glucose-lowering medications.[127,128] The safety and efficacy of diabetes mellitus therapies in HF, including metformin, sulfonylureas, insulin, and glucagon-like peptide analogues, await further data from prospective clinical trials.[129–131] Treatment with thiazolidinediones (eg, rosiglitazone) is associated with fluid retention in patients with HF[129,132] and should be avoided in patients with NYHA class II through IV HF.

5.3.3. Thyroid Disease

Hyperthyroidism has been implicated in causing DCM but most commonly occurs with persistent sinus tachycardia or AF and may be related to tachycardia.[133] Abnormalities in cardiac systolic and diastolic performance have been reported in hypothyroidism. However, the classic findings of myxedema do not usually indicate cardiomyopathy. The low cardiac output results from bradycardia, decreased ventricular filling, reduced cardiac contractility, and diminished myocardial work.[133,134]

5.3.4. Acromegaly and Growth Hormone Deficiency

Impaired cardiovascular function has been associated with reduced life expectancy in patients with growth hormone deficiency and excess. Experimental and clinical studies implicate growth hormone and insulin-like growth factor I in cardiac development.[135] Cardiomyopathy associated with acromegaly is characterized by myocardial hypertrophy with interstitial fibrosis, lympho-mononuclear infiltration, myocyte necrosis, and biventricular concentric hypertrophy.[135]

Table 5. Screening of Family Members and Genetic Testing in Patients With Idiopathic or Familial DCM

Condition	Screening of Family Members	Genetic Testing
Familial DCM	• First-degree relatives not known to be affected should undergo periodic, serial echocardiographic screening with assessment of LV function and size. • Frequency of screening is uncertain, but every 3–5 y is reasonable.[118]	• Genetic testing may be considered in conjunction with genetic counseling.[118,121–123]
Idiopathic DCM	• Patients should inform first-degree relatives of their diagnosis. • Relatives should update their clinicians and discuss whether they should undergo screening by echocardiography.	• The utility of genetic testing in this setting remains uncertain. • Yield of genetic testing may be higher in patients with significant cardiac conduction disease and/or a family history of premature sudden cardiac death.[118,121–123]

DCM indicates dilated cardiomyopathy; and LV, left ventricular.

5.4. Toxic Cardiomyopathy

5.4.1. Alcoholic Cardiomyopathy

Chronic alcoholism is one of the most important causes of DCM.[136] The clinical diagnosis is suspected when biventricular dysfunction and dilatation are persistently observed in a heavy drinker in the absence of other known causes for myocardial disease. Alcoholic cardiomyopathy most commonly occurs in men 30 to 55 years of age who have been heavy consumers of alcohol for >10 years.[137] Women represent approximately 14% of the alcoholic cardiomyopathy cases but may be more vulnerable with less lifetime alcohol consumption.[136,138] The risk of asymptomatic alcoholic cardiomyopathy is increased in those consuming >90 g of alcohol per day (approximately 7 to 8 standard drinks per day) for >5 years.[137] Interestingly, in the general population, mild to moderate alcohol consumption has been reported to be protective against development of HF.[139,140] These paradoxical findings suggest that duration of exposure and individual genetic susceptibility play an important role in pathogenesis. Recovery of LV function after cessation of drinking has been reported.[141] Even if LV dysfunction persists, the symptoms and signs of HF improve after abstinence.[141]

5.4.2. Cocaine Cardiomyopathy

Long-term abuse of cocaine may result in DCM even without CAD, vasculitis, or MI. Depressed LV function has been reported in 4% to 18% of asymptomatic cocaine abusers.[142–144] The safety and efficacy of beta blockers for chronic HF due to cocaine use are unknown.[145]

5.4.3. Cardiotoxicity Related to Cancer Therapies

Several cytotoxic antineoplastic drugs, especially the anthracyclines, are cardiotoxic and can lead to long-term cardiac morbidity. Iron-chelating agents that prevent generation of oxygen free radicals, such as dexrazoxane, are cardioprotective,[146,147] and reduce the occurrence and severity of anthracycline-induced cardiotoxicity and development of HF.

Other antineoplastic chemotherapies with cardiac toxicity are the monoclonal antibody trastuzumab (Herceptin), high-dose cyclophosphamide, taxoids, mitomycin-C, 5-fluorouracil, and the interferons.[148] In contrast to anthracycline-induced cardiac toxicity, trastuzumab-related cardiac dysfunction does not appear to increase with cumulative dose, nor is it associated with ultrastructural changes in the myocardium. However, concomitant anthracycline therapy significantly increases the risk for cardiotoxicity during trastuzumab treatment. The cardiac dysfunction associated with trastuzumab is most often reversible on discontinuation of treatment and initiation of standard medical therapy for HF.[149] The true incidence and reversibility of chemotherapy-related cardiotoxicity are not well documented, and meaningful interventions to prevent injury have not yet been elucidated.

5.4.4. Other Myocardial Toxins and Nutritional Causes of Cardiomyopathy

In addition to the classic toxins described above, a number of other toxic agents may lead to LV dysfunction and HF, including ephedra, cobalt, anabolic steroids, chloroquine, clozapine, amphetamine, methylphenidate, and catecholamines.[150] Ephedra, which has been used for athletic performance enhancement and weight loss, was ultimately banned by the US Food and Drug Administration for its high rate of adverse cardiovascular outcomes, including LV systolic dysfunction, development of HF, and sudden cardiac death (SCD).[151]

Primary and secondary nutritional deficiencies may lead to cardiomyopathy. Chronic alcoholism, anorexia nervosa, AIDS, and pregnancy can account for other rare causes of thiamine deficiency–related cardiomyopathy in the western world.[152] Deficiency in L-carnitine, a necessary cofactor for fatty acid oxidation, may be associated with a syndrome of progressive skeletal myopathy and cardiomyopathy.[153]

5.5. Tachycardia-Induced Cardiomyopathy

Tachycardia-induced cardiomyopathy is a reversible cause of HF characterized by LV myocardial dysfunction caused by increased ventricular rate. The degree of dysfunction correlates with the duration and rate of the tachyarrhythmia. Virtually any supraventricular tachycardia with a rapid ventricular response may induce cardiomyopathy. Ventricular arrhythmias, including frequent premature ventricular complexes, may also induce cardiomyopathy. Maintenance of sinus rhythm or control of ventricular rate is critical to treating patients with tachycardia-induced cardiomyopathy.[154] Reversibility of the cardiomyopathy with treatment of the arrhythmia is the rule, although this may not be complete in all cases. The underlying mechanisms for this are not well understood.

Ventricular pacing at high rates may cause cardiomyopathy. Additionally, right ventricular pacing alone may exacerbate HF symptoms, increase hospitalization for HF, and increase mortality.[155,156] Use of CRT in patients with a conduction delay due to pacing may result in improved LV function and functional capacity.

5.6. Myocarditis and Cardiomyopathies Due to Inflammation

5.6.1. Myocarditis

Inflammation of the heart may cause HF in about 10% of cases of initially unexplained cardiomyopathy.[105,157] A variety of infectious organisms, as well as toxins and medications, most often postviral in origin, may cause myocarditis. In addition, myocarditis is also seen as part of other systemic diseases such as systemic lupus erythematosus and other myocardial muscle diseases such as HIV cardiomyopathy and possibly peripartum cardiomyopathy. Presentation may be acute, with a distinct onset, severe hemodynamic compromise, and severe LV dysfunction as seen in acute fulminant myocarditis, or it may be subacute, with an indistinct onset and better-tolerated LV dysfunction.[158] Prognosis varies, with spontaneous complete resolution (paradoxically most often seen with acute fulminant myocarditis)[158] to the development of DCM despite immunosuppressive therapy.[159] The role of immunosuppressive therapy is controversial.[159] Targeting such therapy to specific individuals based on the presence or absence of viral genome in myocardial biopsy samples may improve response to immunosuppressive therapy.[160]

Giant cell myocarditis is a rare form of myocardial inflammation characterized by fulminant HF, often associated with refractory ventricular arrhythmias and a poor prognosis.[161,162]

Histologic findings include diffuse myocardial necrosis with numerous multinucleated giant cells without granuloma formation. Consideration for advanced HF therapies, including immunosuppression, mechanical circulatory support (MCS), and transplantation, is warranted.

5.6.2. Acquired Immunodeficiency Syndrome

The extent of immunodeficiency influences the incidence of HIV-associated DCM.[163–165] In long-term echocardiographic follow-up,[166] 8% of initially asymptomatic HIV-positive patients were diagnosed with DCM during the 5-year follow-up. Whether early treatment with ACE inhibitors and/or beta blockers will prevent or delay disease progression in these patients is unknown at this time.

5.6.3. Chagas Disease

Although Chagas disease is a relatively uncommon cause of DCM in North America, it remains an important cause of death in Central and South America.[167] Symptomatic chronic Chagas disease develops in an estimated 10% to 30% of infected persons, years or even decades after the *Trypanosoma cruzi* infection. Cardiac changes may include biventricular enlargement, thinning or thickening of ventricular walls, apical aneurysms, and mural thrombi. The conduction system is often affected, typically resulting in right bundle-branch block, left anterior fascicular block, or complete atrioventricular block.

5.7. Inflammation-Induced Cardiomyopathy: Noninfectious Causes

5.7.1. Hypersensitivity Myocarditis

Hypersensitivity to a variety of agents may result in allergic reactions that involve the myocardium, characterized by peripheral eosinophilia and a perivascular infiltration of the myocardium by eosinophils, lymphocytes, and histiocytes. A variety of drugs, most commonly the sulfonamides, penicillins, methyldopa, and other agents such as amphotericin B, streptomycin, phenytoin, isoniazid, tetanus toxoid, hydrochlorothiazide, dobutamine, and chlorthalidone, have been reported to cause allergic hypersensitivity myocarditis.[168] Most patients are not clinically ill but may die suddenly, presumably secondary to an arrhythmia.

5.7.2. Rheumatological/Connective Tissue Disorders

Along with a number of cardiac abnormalities (eg, pericarditis, pericardial effusion, conduction system abnormalities, including complete atrioventricular heart block), DCM can be a rare manifestation of systemic lupus erythematosus and usually correlates with disease activity.[169] Studies suggest that echocardiographic evidence of abnormal LV filling may reflect the presence of myocardial fibrosis and could be a marker of subclinical myocardial involvement in systemic lupus erythematosus patients.[170]

Scleroderma is a rare cause of DCM. One echocardiographic study showed that despite normal LV dimensions or fractional shortening, subclinical systolic impairment was present in the majority of patients with scleroderma.[171] Cardiac involvement in rheumatoid arthritis generally is in the form of myocarditis and/or pericarditis, and development of DCM is rare.[172] Myocardial involvement in rheumatoid arthritis is thought to be secondary to microvasculitis and subsequent microcirculatory disturbances. Myocardial disease in rheumatoid arthritis can occur in the absence of clinical symptoms or abnormalities of the electrocardiogram (ECG).[173]

5.8. Peripartum Cardiomyopathy

Peripartum cardiomyopathy is a disease of unknown cause in which LV dysfunction occurs during the last trimester of pregnancy or the early puerperium. It is reported in 1:1300 to 1:4000 live births.[174] Risk factors for peripartum cardiomyopathy include advanced maternal age, multiparity, African descent, and long-term tocolysis. Although its etiology remains unknown, most theories have focused on hemodynamic and immunologic causes.[174] The prognosis of peripartum cardiomyopathy is related to the recovery of ventricular function. Significant improvement in myocardial function is seen in 30% to 50% of patients in the first 6 months after presentation.[174] However, for those patients who do not recover to normal or near-normal function, the prognosis is similar to other forms of DCM.[175] Cardiomegaly that persists for >4 to 6 months after diagnosis indicates a poor prognosis, with a 50% mortality rate at 6 years. Subsequent pregnancy in women with a history of peripartum cardiomyopathy may be associated with a further decrease in LV function and can result in clinical deterioration, including death. However, if ventricular function has normalized in women with a history of peripartum cardiomyopathy, the risk may be less.[174] There is an increased risk of venous thromboembolism, and anticoagulation is recommended, especially if ventricular dysfunction is persistent.

5.9. Cardiomyopathy Caused By Iron Overload

Iron overload cardiomyopathy manifests itself as systolic or diastolic dysfunction secondary to increased deposition of iron in the heart and occurs with common genetic disorders such as primary hemochromatosis or with lifetime transfusion requirements as seen in beta-thalassemia major.[176] Hereditary hemochromatosis, an autosomal recessive disorder, is the most common hereditary disease of Northern Europeans, with a prevalence of approximately 5 per 1000. The actuarial survival rates of persons who are homozygous for the mutation of the hemochromatosis gene *C282Y* have been reported to be 95%, 93%, and 66%, at 5, 10, and 20 years, respectively.[177] Similarly, in patients with thalassemia major, cardiac failure is one of the most frequent causes of death. Chelation therapy, including newer forms of oral chelators, such as deferoxamine, and phlebotomy, have dramatically improved the outcome of hemochromatosis, and the roles of gene therapy, hepcidin, and calcium channel blockers are being actively investigated.[178]

5.10. Amyloidosis

Cardiac amyloidosis involves the deposition of insoluble proteins as fibrils in the heart, resulting in HF. Primary or AL amyloidosis (monoclonal kappa or lambda light chains), secondary amyloidosis (protein A), familial TTR amyloidosis (mutant transthyretin), dialysis-associated amyloidosis (beta-2-microglobulin), or senile TTR amyloidosis (wild-type transthyretin) can affect the heart, but cardiac involvement is primarily encountered in AL and TTR amyloidosis.[179] The disease can be rapidly progressive, and in patients with ventricular septum thickness >15 mm, LVEF <40%, and symptoms of HF, median survival may be <6 months.[180] Cardiac

biomarkers (eg, B-type natriuretic peptide [BNP], cardiac troponin) have been reported to predict response and progression of disease and survival.[181] Three percent to 4% of African Americans carry an amyloidogenic allele of the human serum protein transthyretin (TTR V122I), which appears to increase risk for cardiac amyloid deposition after 65 years of age.[182]

5.11. Cardiac Sarcoidosis

Cardiac sarcoidosis is an underdiagnosed disease that may affect as many as 25% of patients with systemic sarcoidosis. Although most commonly recognized in patients with other manifestations of sarcoidosis, cardiac involvement may occur in isolation and go undetected. Cardiac sarcoidosis may present as asymptomatic LV dysfunction, HF, atrioventricular block, atrial or ventricular arrhythmia, and SCD.[183] Although untested in clinical trials, early use of high-dose steroid therapy may halt or reverse cardiac damage.[184] Cardiac magnetic resonance and cardiac positron emission tomographic scanning can identify cardiac involvement with patchy areas of myocardial inflammation and fibrosis. In the setting of ventricular tachyarrhythmia, patients may require placement of an implantable cardioverter-defibrillator (ICD) for primary prevention of SCD.[185]

5.12. Stress (Takotsubo) Cardiomyopathy

Stress cardiomyopathy is characterized by acute reversible LV dysfunction in the absence of significant CAD, triggered by acute emotional or physical stress.[23] This phenomenon is identified by a distinctive pattern of "apical ballooning," first described in Japan as takotsubo, and often affects postmenopausal women.[186] A majority of patients have a clinical presentation similar to that of acute coronary syndrome (ACS) and may have transiently elevated cardiac enzymes.

6. Initial and Serial Evaluation of the HF Patient

6.1. Clinical Evaluation

6.1.1. History and Physical Examination: Recommendations

Class I

1. **A thorough history and physical examination should be obtained/performed in patients presenting with HF to identify cardiac and noncardiac disorders or behaviors that might cause or accelerate the development or progression of HF.** ***(Level of Evidence: C)***
2. **In patients with idiopathic DCM, a 3-generational family history should be obtained to aid in establishing the diagnosis of familial DCM.** ***(Level of Evidence: C)***
3. **Volume status and vital signs should be assessed at each patient encounter. This includes serial assessment of weight, as well as estimates of jugular venous pressure and the presence of peripheral edema or orthopnea.[187–190]** ***(Level of Evidence: B)***

Despite advances in imaging technology and increasing availability of diagnostic laboratory testing, a careful history and physical examination remain the cornerstones in the assessment of patients with HF. The components of a focused history and physical examination for the patient with HF are listed in Table 6. The history provides clues to the etiology of the cardiomyopathy, including the diagnosis of familial cardiomyopathy (defined as ≥2 relatives with idiopathic DCM). Familial syndromes are now recognized to occur in 20% to 35% of patients with apparent idiopathic DCM[118]; thus, a 3-generation family history should be obtained. The history also provides information about the severity of the disease and the patient's prognosis and identifies opportunities for therapeutic interventions. The physical examination provides information about the severity of illness and allows assessment of volume status and adequacy of perfusion. In advanced HF*r*EF, orthopnea and jugular venous pressure are useful findings to detect elevated LV filling pressures.[187,189,190]

See Online Data Supplements 5, 6, and 7 for additional data on stress testing and clinical evaluation.

6.1.2. Risk Scoring: Recommendation

Class IIa

1. **Validated multivariable risk scores can be useful to estimate subsequent risk of mortality in ambulatory or hospitalized patients with HF.[199–207]** ***(Level of Evidence: B)***

In the course of standard evaluation, clinicians should routinely assess the patient's potential for adverse outcome, because accurate risk stratification may help guide therapeutic decision making, including a more rapid transition to advanced HF therapies. A number of methods objectively assess risk, including biomarker testing (Section 6.3), as well as a variety of multivariable clinical risk scores (Table 7); these risk scores are for use in ambulatory[199,203,205,206,208] and hospitalized patients.[200,202,204,205,209] Risk models specifically for patients with HF*p*EF have also been described.[201]

One well-validated risk score, the Seattle Heart Failure Model, is available in an interactive application on the Internet[210] and provides robust information about risk of mortality in ambulatory patients with HF. For patients hospitalized with acutely decompensated HF, the model developed by ADHERE (Acute Decompensated Heart Failure National Registry) incorporates 3 routinely measured variables on hospital admission (ie, systolic blood pressure, blood urea nitrogen, and serum creatinine) and stratifies subjects into categories with a 10-fold range of crude in-hospital mortality (from 2.1% to 21.9%).[200] Notably, clinical risk scores have not performed as well in estimating risk of hospital readmission.[211] For this purpose, biomarkers such as natriuretic peptides hold considerable promise[212,213] (Section 6.3).

See Online Data Supplement 8 for additional data on clinical evaluation risk scoring.

6.2. Diagnostic Tests: Recommendations

Class I

1. **Initial laboratory evaluation of patients presenting with HF should include complete blood count,**

Table 6. History and Physical Examination in HF

	Comments
History	
Potential clues suggesting etiology of HF	A careful family history may identify an underlying familial cardiomyopathy in patients with idiopathic DCM.[118] Other etiologies outlined in Section 5 should be considered as well.
Duration of illness	A patient with recent-onset systolic HF may recover over time.[113]
Severity and triggers of dyspnea and fatigue, presence of chest pain, exercise capacity, physical activity, sexual activity	To determine NYHA class; identify potential symptoms of coronary ischemia.
Anorexia and early satiety, weight loss	Gastrointestinal symptoms are common in patients with HF. Cardiac cachexia is associated with adverse prognosis.[191]
Weight gain	Rapid weight gain suggests volume overload.
Palpitations, (pre)syncope, ICD shocks	Palpitations may be indications of paroxysmal AF or ventricular tachycardia. ICD shocks are associated with adverse prognosis.[192]
Symptoms suggesting transient ischemic attack or thromboembolism	Affects consideration of the need for anticoagulation.
Development of peripheral edema or ascites	Suggests volume overload.
Disordered breathing at night, sleep problems	Treatment for sleep apnea may improve cardiac function and decrease pulmonary hypertension.[193]
Recent or frequent prior hospitalizations for HF	Associated with adverse prognosis.[194]
History of discontinuation of medications for HF	Determine whether lack of GDMT in patients with HF*r*EF reflects intolerance, an adverse event, or perceived contraindication to use. Withdrawal of these medications has been associated with adverse prognosis.[195,196]
Medications that may exacerbate HF	Removal of such medications may represent a therapeutic opportunity.
Diet	Awareness and restriction of sodium and fluid intake should be assessed.
Adherence to medical regimen	Access to medications; family support; access to follow-up; cultural sensitivity
Physical Examination	
BMI and evidence of weight loss	Obesity may be a contributing cause of HF; cachexia may correspond with poor prognosis.
Blood pressure (supine and upright)	Assess for hypertension or hypotension. Width of pulse pressure may reflect adequacy of cardiac output. Response of blood pressure to Valsalva maneuver may reflect LV filling pressures.[197]
Pulse	Manual palpation will reveal strength and regularity of pulse rate.
Examination for orthostatic changes in blood pressure and heart rate	Consistent with volume depletion or excess vasodilation from medications.
Jugular venous pressure at rest and following abdominal compression (http://wn.com/jugular_venous_distension_example)	Most useful finding on physical examination to identify congestion.[187–190,198]
Presence of extra heart sounds and murmurs	S_3 is associated with adverse prognosis in HF*r*EF.[188] Murmurs may be suggestive of valvular heart disease.
Size and location of point of maximal impulse	Enlarged and displaced point of maximal impulse suggests ventricular enlargement.
Presence of right ventricular heave	Suggests significant right ventricular dysfunction and/or pulmonary hypertension.
Pulmonary status: respiratory rate, rales, pleural effusion	In advanced chronic HF, rales are often absent despite major pulmonary congestion.
Hepatomegaly and/or ascites	Usually markers of volume overload.
Peripheral edema	Many patients, particularly those who are young, may be not edematous despite intravascular volume overload. In obese patients and elderly patients, edema may reflect peripheral rather than cardiac causes.
Temperature of lower extremities	Cool lower extremities may reflect inadequate cardiac output.

AF indicates atrial fibrillation; BMI, body mass index; DCM, dilated cardiomyopathy; GDMT, guideline-directed medical therapy; HF, heart failure; HF*r*EF, heart failure with reduced ejection fraction; ICD, implantable cardioverter-defibrillator; LV, left ventricular; and NYHA, New York Heart Association.

urinalysis, serum electrolytes (including calcium and magnesium), blood urea nitrogen, serum creatinine, glucose, fasting lipid profile, liver function tests, and thyroid-stimulating hormone. ***(Level of Evidence: C)***

2. **Serial monitoring, when indicated, should include serum electrolytes and renal function.** ***(Level of Evidence: C)***
3. **A 12-lead ECG should be performed initially on all patients presenting with HF.** ***(Level of Evidence: C)***

Class IIa

1. **Screening for hemochromatosis or HIV is reasonable in selected patients who present with HF.[216]** ***(Level of Evidence: C)***
2. **Diagnostic tests for rheumatologic diseases, amyloidosis, or pheochromocytoma are reasonable in patients presenting with HF in whom there is a clinical suspicion of these diseases.** ***(Level of Evidence: C)***

Table 7. Selected Multivariable Risk Scores to Predict Outcome in HF

Risk Score	Reference/Link
Chronic HF	
All patients with chronic HF	
Seattle Heart Failure Model	203/http://SeattleHeartFailureModel.org
Heart Failure Survival Score	199/http://handheld.softpedia.com/get/Health/Calculator/HFSS-Calc-37354.shtml
CHARM Risk Score	206
CORONA Risk Score	207
Specific to chronic HF*p*EF	
I-PRESERVE Score	201
Acutely decompensated HF	
ADHERE Classification and Regression Tree (CART) Model	200
American Heart Association Get With The Guidelines Score	205/http://www.heart.org/HEARTORG/HealthcareProfessional/GetWithTheGuidelinesHFStroke/GetWithTheGuidelinesHeartFailureHomePage/Get-With-The-Guidelines-Heart-Failure-Home-%20Page_UCM_306087_SubHomePage.jsp
EFFECT Risk Score	202/http://www.ccort.ca/Research/CHFRiskModel.aspx
ESCAPE Risk Model and Discharge Score	214
OPTIMIZE HF Risk-Prediction Nomogram	215

ADHERE indicates Acute Decompensated Heart Failure National Registry; CHARM, Candesartan in Heart failure-Assessment of Reduction in Mortality and morbidity; CORONA, Controlled Rosuvastatin Multinational Trial in Heart Failure; EFFECT, Enhanced Feedback for Effective Cardiac Treatment; ESCAPE, Evaluation Study of Congestive Heart Failure and Pulmonary Artery Catheterization Effectiveness; HF, heart failure; HF*p*EF, heart failure with preserved ejection fraction; I-PRESERVE, Irbesartan in Heart Failure with Preserved Ejection Fraction Study; and OPTIMIZE, Organized Program to Initiate Lifesaving Treatment in Hospitalized Patients with Heart Failure.

6.3. Biomarkers: Recommendations

A. Ambulatory/Outpatient

Class I

1. **In ambulatory patients with dyspnea, measurement of BNP or N-terminal pro-B-type natriuretic peptide (NT-proBNP) is useful to support clinical decision making regarding the diagnosis of HF, especially in the setting of clinical uncertainty.[217–223] *(Level of Evidence: A)***
2. **Measurement of BNP or NT-proBNP is useful for establishing prognosis or disease severity in chronic HF.[222,224–229] *(Level of Evidence: A)***

Class IIa

1. **BNP- or NT-proBNP–guided HF therapy can be useful to achieve optimal dosing of GDMT in select clinically euvolemic patients followed in a well-structured HF disease management program.[230–237] *(Level of Evidence: B)***

Class IIb

1. **The usefulness of serial measurement of BNP or NT-proBNP to reduce hospitalization or mortality in patients with HF is not well established.[230–237] *(Level of Evidence: B)***
2. **Measurement of other clinically available tests such as biomarkers of myocardial injury or fibrosis may be considered for additive risk stratification in patients with chronic HF.[238–244] *(Level of Evidence: B)***

B. Hospitalized/Acute

Class I

1. **Measurement of BNP or NT-proBNP is useful to support clinical judgment for the diagnosis of acutely decompensated HF, especially in the setting of uncertainty for the diagnosis.[212,245–250] *(Level of Evidence: A)***
2. **Measurement of BNP or NT-proBNP and/or cardiac troponin is useful for establishing prognosis or disease severity in acutely decompensated HF.[248,251–258] *(Level of Evidence: A)***

Class IIb

1. **The usefulness of BNP- or NT-proBNP–guided therapy for acutely decompensated HF is not well established.[259,260] *(Level of Evidence: C)***
2. **Measurement of other clinically available tests such as biomarkers of myocardial injury or fibrosis may be considered for additive risk stratification in patients with acutely decompensated HF.[248,253,256,257,261–267] *(Level of Evidence: A)***

In addition to routine clinical laboratory tests, other biomarkers are gaining greater attention for their utility in HF management. These biomarkers may reflect various pathophysiological aspects of HF, including myocardial wall stress, hemodynamic abnormalities, inflammation, myocyte injury, neurohormonal upregulation, and myocardial remodeling, as well as extracellular matrix turnover. Thus, these biomarkers are potentially powerful adjuncts to current standards for the diagnosis, prognosis, and treatment of acute and chronic HF.

6.3.1. Natriuretic Peptides: BNP or NT-proBNP

BNP or its amino-terminal cleavage equivalent (NT-proBNP) is derived from a common 108-amino acid precursor peptide ($proBNP_{108}$) that is generated by cardiomyocytes in the context of numerous triggers, most notably myocardial stretch. Following several steps of processing, BNP and NT-proBNP are released from the cardiomyocyte, along with variable amounts of $proBNP_{108}$, the latter of which is detected by all assays that measure either "BNP" or "NT-proBNP."

Assays for BNP and NT-proBNP have been increasingly used to establish the presence and severity of HF. In general, BNP and NT-proBNP values are reasonably correlated, and either can be used in patient care settings as long as their respective absolute values and cut points are not used interchangeably. BNP and NT-proBNP are useful to support clinical judgment for the diagnosis or exclusion of HF, in the setting of chronic ambulatory HF[217–223] or acute decompensated HF[245–250]; the value of natriuretic peptide testing is particularly significant when the etiology of dyspnea is unclear.

Although lower values of BNP or NT-proBNP exclude the presence of HF and higher values have reasonably high positive predictive value to diagnose HF, clinicians should be aware that elevated plasma levels for both natriuretic peptides have been associated with a wide variety of cardiac and noncardiac causes (Table 8).[268–271]

BNP and NT-proBNP levels improve with treatment of chronic HF,[225,272–274] with lowering of levels over time in general, correlating with improved clinical outcomes.[248,251,254,260] Thus, BNP or NT-proBNP "guided" therapy has been studied against standard care without natriuretic peptide measurement to determine whether guided therapy renders superior achievement of GDMT in patients with HF. However, RCTs have yielded inconsistent results.

The positive and negative natriuretic peptide–guided therapy trials differ primarily in their study populations, with successful trials enrolling younger patients and only those with HF*r*EF. In addition, a lower natriuretic peptide goal and/or a substantial reduction in natriuretic peptides during treatment are consistently present in the positive "guided" therapy trials.[275] Although most trials examining the strategy of biomarker "guided" HF management were small and underpowered, 2 comprehensive meta-analyses concluded that BNP-guided therapy reduces all-cause mortality in patients with chronic HF compared with usual clinical care,[231,232] especially in patients <75 years of age. This survival benefit may be attributed to increased achievement of GDMT. In some cases, BNP or NT-proBNP levels may not be easily modifiable. If the BNP or NT-proBNP value does not fall after aggressive HF care, risk for death or hospitalization for HF is significant. On the other hand, some patients with advanced HF have normal BNP or NT-proBNP levels or have falsely low BNP levels because of obesity and HF*p*EF. All of these patients should still receive appropriate GDMT.

Table 8. Selected Causes of Elevated Natriuretic Peptide Concentrations

Cardiac
• Heart failure, including RV syndromes
• Acute coronary syndrome
• Heart muscle disease, including LVH
• Valvular heart disease
• Pericardial disease
• Atrial fibrillation
• Myocarditis
• Cardiac surgery
• Cardioversion
Noncardiac
• Advancing age
• Anemia
• Renal failure
• Pulmonary: obstructive sleep apnea, severe pneumonia, pulmonary hypertension
• Critical illness
• Bacterial sepsis
• Severe burns
• Toxic-metabolic insults, including cancer chemotherapy and envenomation

LVH indicates left ventricular hypertrophy; and RV, right ventricular.

6.3.2. Biomarkers of Myocardial Injury: Cardiac Troponin T or I

Abnormal concentrations of circulating cardiac troponin are found in patients with HF, often without obvious myocardial ischemia and frequently in those without underlying CAD. This suggests ongoing myocyte injury or necrosis in these patients.[238–241,276] In chronic HF, elaboration of cardiac troponins is associated with impaired hemodynamics,[238] progressive LV dysfunction,[239] and increased mortality rates.[238–241,276] Similarly, in patients with acute decompensated HF, elevated cardiac troponin levels are associated with worse clinical outcomes and mortality[253,257,263]; decrease in troponin levels over time with treatment is associated with a better prognosis than persistent elevation in patients with chronic[239] or acute HF.[277] Given the tight association with ACS and troponin elevation as well as the link between MI and the development of acute HF,[278] the measurement of troponin I or T should be routine in patients presenting with acutely decompensated HF syndromes.

6.3.3. Other Emerging Biomarkers

Besides natriuretic peptides or troponins, multiple other biomarkers, including those reflecting inflammation, oxidative stress, neurohormonal disarray, and myocardial and matrix remodeling, have been widely examined for their prognostic value in HF. Biomarkers of myocardial fibrosis, soluble ST2 and galectin-3 are not only predictive of hospitalization and death in patients with HF but also additive to natriuretic peptide levels in their prognostic value. Markers of renal injury may also offer additional prognostic value because renal function or injury may be involved in the pathogenesis, progression, decompensation, or complications in chronic or acute decompensated HF.[242–244,264,265,279] Strategies that combine multiple biomarkers may ultimately prove beneficial in guiding HF therapy in the future.

See Table 9 for a summary of recommendations from this section.

6.4. Noninvasive Cardiac Imaging: Recommendations

See Table 10 for a summary of recommendations from this section.

Table 9. Recommendations for Biomarkers in HF

Biomarker, Application	Setting	COR	LOE	References
Natriuretic peptides				
Diagnosis or exclusion of HF	Ambulatory, Acute	I	A	212, 217–223, 245–250
Prognosis of HF	Ambulatory, Acute	I	A	222, 224–229, 248, 251–258
Achieve GDMT	Ambulatory	IIa	B	230–237
Guidance for acutely decompensated HF therapy	Acute	IIb	C	259, 260
Biomarkers of myocardial injury				
Additive risk stratification	Acute, Ambulatory	I	A	238–241, 248, 253, 256–267
Biomarkers of myocardial fibrosis				
Additive risk stratification	Ambulatory	IIb	B	242–244
	Acute	IIb	A	248, 253, 256, 258–260, 262, 264–267

COR indicates Class of Recommendation; GDMT, guideline-directed medical therapy; HF, heart failure; and LOE, Level of Evidence.

Class I

1. **Patients with suspected or new-onset HF, or those presenting with acute decompensated HF, should undergo a chest x-ray to assess heart size and pulmonary congestion and to detect alternative cardiac, pulmonary, and other diseases that may cause or contribute to the patient's symptoms.** ***(Level of Evidence: C)***
2. **A 2-dimensional echocardiogram with Doppler should be performed during initial evaluation of patients presenting with HF to assess ventricular function, size, wall thickness, wall motion, and valve function.** ***(Level of Evidence: C)***
3. **Repeat measurement of EF and measurement of the severity of structural remodeling are useful to provide information in patients with HF who have had a significant change in clinical status; who have experienced or recovered from a clinical event; or who have received treatment, including GDMT, that might have had a significant effect on cardiac function; or who may be candidates for device therapy.** ***(Level of Evidence: C)***

Class IIa

1. **Noninvasive imaging to detect myocardial ischemia and viability is reasonable in patients presenting with de novo HF, who have known CAD and no angina, unless the patient is not eligible for revascularization of any kind.** ***(Level of Evidence: C)***
2. **Viability assessment is reasonable in select situations when planning revascularization in HF patients with CAD.[281–285]** ***(Level of Evidence: B)***
3. **Radionuclide ventriculography or magnetic resonance imaging can be useful to assess LVEF and volume when echocardiography is inadequate.** ***(Level of Evidence: C)***
4. **Magnetic resonance imaging is reasonable when assessing myocardial infiltrative processes or scar burden.[286–288]** ***(Level of Evidence: B)***

Class III: No Benefit

1. **Routine repeat measurement of LV function assessment in the absence of clinical status change or treatment interventions should not be performed.[289,290]** ***(Level of Evidence: B)***

Table 10. Recommendations for Noninvasive Cardiac Imaging

Recommendations	COR	LOE
Patients with suspected, acute, or new-onset HF should undergo a chest x-ray	I	C
A 2-dimensional echocardiogram with Doppler should be performed for initial evaluation of HF	I	C
Repeat measurement of EF is useful in patients with HF who have had a significant change in clinical status or received treatment that might affect cardiac function or for consideration of device therapy	I	C
Noninvasive imaging to detect myocardial ischemia and viability is reasonable in HF and CAD	IIa	C
Viability assessment is reasonable before revascularization in HF patients with CAD	IIa	B[281–285]
Radionuclide ventriculography or MRI can be useful to assess LVEF and volume	IIa	C
MRI is reasonable when assessing myocardial infiltration or scar	IIa	B[286–288]
Routine repeat measurement of LV function assessment should not be performed	III: No Benefit	B[289,290]

CAD indicates coronary artery disease; COR, Class of Recommendation; EF, ejection fraction; HF, heart failure; LOE, Level of Evidence; LV, left ventricular; LVEF, left ventricular ejection fraction; and MRI, magnetic resonance imaging.

The chest x-ray is important for the evaluation of patients presenting with signs and symptoms of HF because it assesses cardiomegaly and pulmonary congestion and may reveal alternative causes, cardiopulmonary or otherwise, of the patient's symptoms. Apart from congestion, however, other findings on chest x-ray are associated with HF only in the context of clinical presentation. Cardiomegaly may be absent in HF. A chest x-ray may also show other cardiac chamber enlargement, increased pulmonary venous pressure, interstitial or alveolar edema, valvular or pericardial calcification, or coexisting thoracic diseases. Considering its low sensitivity and specificity, the chest x-ray should not be the sole determinant of the specific cause of HF. Moreover, a supine chest x-ray has limited value in acute decompensated HF.

Although a complete history and physical examination are important first steps, the most useful diagnostic test in the evaluation of patients with or at risk for HF (eg, postacute MI) is a comprehensive 2-dimensional echocardiogram; coupled with Doppler flow studies, the transthoracic echocardiogram can identify abnormalities of myocardium, heart valves, and pericardium. Echocardiography can reveal subclinical HF and predict risk of subsequent events.[291–295] Use of echocardiograms in patients with suspected HF improves disease identification and provision of appropriate medical care.[296]

Echocardiographic evaluation should address whether LVEF is reduced, LV structure is abnormal, and other structural abnormalities are present that could account for the clinical presentation. This information should be quantified, including numerical estimates of EF measurement, ventricular dimensions, wall thickness, calculations of ventricular volumes, and evaluation of chamber geometry and regional wall motion. Documentation of LVEF is an HF quality-of-care performance measure.[297] Right ventricular size and function as well as atrial size and dimensions should also be measured. All valves should be evaluated for anatomic and flow abnormalities. Secondary changes, particularly the severity of mitral and tricuspid valve insufficiency, should be determined. Noninvasive hemodynamic data constitute important additional information. Mitral valve inflow pattern, pulmonary venous inflow pattern, and mitral annular velocity provide data about LV filling and left atrial pressure. The tricuspid valve regurgitant gradient, coupled with measurement of inferior vena cava diameter and its response during respiration, provides estimates of systolic pulmonary artery pressure and central venous pressure. Many of these abnormalities are prognostically important and can be present without manifest HF.

Serial echocardiographic evaluations are useful because evidence of cardiac reverse remodeling can provide important information in patients who have had a change in clinical status or have experienced or recovered from an event or treatment that affects cardiac function. However, the routine repeat assessment of ventricular function in the absence of changing clinical status or a change in treatment intervention is not indicated.

The preference for echocardiography as an imaging modality is due to its widespread availability and lack of ionizing radiation; however, other imaging modalities may be of use. Magnetic resonance imaging assesses LV volume and EF measurements at least as accurately as echocardiography. However, additional information about myocardial perfusion, viability, and fibrosis from magnetic resonance imaging can help identify HF etiology and assess prognosis.[298] Magnetic resonance imaging provides high anatomical resolution of all aspects of the heart and surrounding structure, leading to its recommended use in known or suspected congenital heart diseases.[5] Cardiac computed tomography can also provide accurate assessment of cardiac structure and function, including the coronary arteries.[299] An advantage of cardiac computed tomography over echocardiography may be its ability to characterize the myocardium, but studies have yet to demonstrate the importance of this factor. Reports of cardiac computed tomography in patients with suspected HF are limited. Furthermore, both cardiac computed tomography and magnetic resonance imaging lose accuracy with high heart rates. Radionuclide ventriculography may also be used for evaluation of cardiac function when other tests are unavailable or inadequate. However, as a planar technique, radionuclide ventriculography cannot directly assess valvular structure, function, or ventricular wall thickness; it may be more useful for assessing LV volumes in patients with significant baseline wall motion abnormalities or distorted geometry. Ventriculography is highly reproducible.[300] Single photon emission computed tomography or positron emission tomography scans are not primarily used to determine LV systolic global and regional function unless these parameters are quantified from the resultant images during myocardial perfusion and/or viability assessment.[301,302] Candidates for coronary revascularization who present with a high suspicion for obstructive CAD should undergo coronary angiography. Stress nuclear imaging or echocardiography may be an acceptable option for assessing ischemia in patients presenting with HF who have known CAD and no angina unless they are ineligible for revascularization.[303] Although the results of the STICH (Surgical Treatment for Ischemic Heart Failure) trial have cast doubt on the role of myocardial viability assessment to determine the mode of therapy,[304] the data are nevertheless predictive of a positive outcome. When these data are taken into consideration with multiple previous studies demonstrating the usefulness of this approach,[281–285] it becomes reasonable to recommend viability assessment when treating patients with HF*r*EF who have known CAD.[14]

See Online Data Supplement 9 for additional data on imaging—echocardiography.

6.5. Invasive Evaluation: Recommendations

See Table 11 for a summary of recommendations from this section.

Class I

1. **Invasive hemodynamic monitoring with a pulmonary artery catheter should be performed to guide therapy in patients who have respiratory distress or clinical evidence of impaired perfusion in whom the adequacy or excess of intracardiac filling pressures cannot be determined from clinical assessment.** ***(Level of Evidence: C)***

Table 11. Recommendations for Invasive Evaluation

Recommendations	COR	LOE
Monitoring with a pulmonary artery catheter should be performed in patients with respiratory distress or impaired systemic perfusion when clinical assessment is inadequate	I	C
Invasive hemodynamic monitoring can be useful for carefully selected patients with acute HF with persistent symptoms and/or when hemodynamics are uncertain	IIa	C
When ischemia may be contributing to HF, coronary arteriography is reasonable	IIa	C
Endomyocardial biopsy can be useful in patients with HF when a specific diagnosis is suspected that would influence therapy	IIa	C
Routine use of invasive hemodynamic monitoring is not recommended in normotensive patients with acute HF	III: No Benefit	B[305]
Endomyocardial biopsy should not be performed in the routine evaluation of HF	III: Harm	C

COR indicates Class of Recommendation; HF, heart failure; and LOE, Level of Evidence.

Class IIa

1. **Invasive hemodynamic monitoring can be useful for carefully selected patients with acute HF who have persistent symptoms despite empiric adjustment of standard therapies and**
   a. **whose fluid status, perfusion, or systemic or pulmonary vascular resistance is uncertain;**
   b. **whose systolic pressure remains low, or is associated with symptoms, despite initial therapy;**
   c. **whose renal function is worsening with therapy;**
   d. **who require parenteral vasoactive agents; or**
   e. **who may need consideration for MCS or transplantation.** ***(Level of Evidence: C)***
2. **When ischemia may be contributing to HF, coronary arteriography is reasonable for patients eligible for revascularization.** ***(Level of Evidence: C)***
3. **Endomyocardial biopsy can be useful in patients presenting with HF when a specific diagnosis is suspected that would influence therapy.** ***(Level of Evidence: C)***

Class III: No Benefit

1. **Routine use of invasive hemodynamic monitoring is not recommended in normotensive patients with acute decompensated HF and congestion with symptomatic response to diuretics and vasodilators.[305]** ***(Level of Evidence: B)***

Class III: Harm

1. **Endomyocardial biopsy should not be performed in the routine evaluation of patients with HF.** ***(Level of Evidence: C)***

6.5.1. Right-Heart Catheterization

There has been no established role for routine or periodic invasive hemodynamic measurements in the management of HF. Most drugs used for the treatment of HF are prescribed on the basis of their ability to improve symptoms or survival rather than their effect on hemodynamic variables. The initial and target doses of these drugs are generally selected on the basis of controlled trial experience rather than changes produced in cardiac output or pulmonary capillary wedge pressure. Hemodynamic monitoring is indicated in patients with clinically indeterminate volume status and those refractory to initial therapy, particularly if intracardiac filling pressures and cardiac output are unclear. Patients with clinically significant hypotension (systolic blood pressure typically <90 mm Hg or symptomatic low systolic blood pressure) and/or worsening renal function during initial therapy might also benefit from invasive hemodynamic measurements.[305,306] Patients being considered for cardiac transplantation or placement of an MCS device are also candidates for complete right-heart catheterization, including an assessment of pulmonary vascular resistance, a necessary part of the initial transplantation evaluation. Invasive hemodynamic monitoring should be performed in patients with 1) presumed cardiogenic shock requiring escalating pressor therapy and consideration of MCS; 2) severe clinical decompensation in which therapy is limited by uncertain contributions of elevated filling pressures, hypoperfusion, and vascular tone; 3) apparent dependence on intravenous inotropic infusions after initial clinical improvement; or 4) persistent severe symptoms despite adjustment of recommended therapies. On the other hand, routine use of invasive hemodynamic monitoring is not recommended in normotensive patients with acute decompensated HF who have a symptomatic response to diuretics and vasodilators. This reinforces the concept that right-heart catheterization is best reserved for those situations where a specific clinical or therapeutic question needs to be addressed.

6.5.2. Left-Heart Catheterization

Left-heart catheterization or coronary angiography is indicated for patients with HF and angina and may be useful for those patients without angina but with LV dysfunction. Invasive coronary angiography should be used in accordance with the ACCF/AHA coronary artery bypass graft (CABG) and percutaneous coronary intervention guidelines[10,12] and should only be performed in patients who are potentially eligible for revascularization.[307–309] In patients with known CAD and angina or with significant ischemia diagnosed by ECG or noninvasive testing and impaired ventricular function, coronary angiography is indicated. Among those without a prior diagnosis, CAD should be considered as a potential etiology of impaired LV function and should be excluded wherever possible. Coronary angiography may be considered in these circumstances to detect and localize large-vessel coronary obstructions. In patients in whom CAD has been excluded as

the cause of LV dysfunction, coronary angiography is generally not indicated unless a change in clinical status suggests interim development of ischemic disease.

6.5.3. Endomyocardial Biopsy

Endomyocardial biopsy can be useful when seeking a specific diagnosis that would influence therapy, and biopsy should thus be considered in patients with rapidly progressive clinical HF or worsening ventricular dysfunction that persists despite appropriate medical therapy. Endomyocardial biopsy should also be considered in patients suspected of having acute cardiac rejection status after heart transplantation or having myocardial infiltrative processes. A specific example is to determine chemotherapy for primary cardiac amyloidosis. Additional other indications for endomyocardial biopsy include in patients with rapidly progressive and unexplained cardiomyopathy, those in whom active myocarditis, especially giant cell myocarditis, is being considered.[310] Routine endomyocardial biopsy is not recommended in all cases of HF, given limited diagnostic yield and the risk of procedure-related complications.

See Online Data Supplement 10 for additional data on biopsy.

7. Treatment of Stages A to D

7.1. Stage A: Recommendations

Class I

1. **Hypertension and lipid disorders should be controlled in accordance with contemporary guidelines to lower the risk of HF.[27,94,311–314] *(Level of Evidence: A)***
2. **Other conditions that may lead to or contribute to HF, such as obesity, diabetes mellitus, tobacco use, and known cardiotoxic agents, should be controlled or avoided. *(Level of Evidence: C)***

7.1.1. Recognition and Treatment of Elevated Blood Pressure

The lifetime risk for development of hypertension is considerable and represents a major public health issue.[97] Elevated blood pressure is a major risk factor for the development of both HF*p*EF and HF*r*EF,[91,92] a risk that extends across all age ranges. Long-term treatment of both systolic and diastolic hypertension has been shown to reduce the risk of incident HF by approximately 50%.[94,311–314] Treatment of hypertension is particularly beneficial in older patients.[311] One trial of a diuretic-based program demonstrated a number needed to treat of 52 to prevent 1 HF event in 2 years.[311] In another study, elderly patients with a history or ECG evidence of prior MI had a >80% risk reduction for incident HF with aggressive blood pressure control.[94] Given the robust outcomes with blood pressure reduction, clinicians should lower both systolic and diastolic blood pressure in accordance with published guidelines.[27]

Choice of antihypertensive therapy should also follow guidelines,[27] with specific options tailored to concomitant medical problems, such as diabetes mellitus or CAD. Diuretic-based antihypertensive therapy has repeatedly been shown to prevent HF in a wide range of patients; ACE inhibitors, ARBs, and beta blockers are also effective. Data are less clear for calcium antagonists and alpha blockers in reducing the risk for incident HF.

7.1.2. Treatment of Dyslipidemia and Vascular Risk

Patients with known atherosclerotic disease are likely to develop HF. Clinicians should seek to control vascular risk factors in such patients according to guidelines.[28] Aggressive treatment of hyperlipidemia with statins reduces the likelihood of HF in at-risk patients.[315,316] Long-term treatment with ACE inhibitors in similar patients may also decrease the risk of HF.[314,317]

7.1.3. Obesity and Diabetes Mellitus

Obesity and overweight have been repeatedly linked to an increased risk for HF.[99,318,319] Presumably, the link between obesity and risk for HF is explained by the clustering of risk factors for heart disease in those with elevated BMI (ie, the metabolic syndrome). Similarly, insulin resistance, with or without diabetes mellitus, is also an important risk factor for the development of HF.[92,320–323] Diabetes mellitus is an especially important risk factor for women and may, in fact, triple the risk for developing HF.[91,324] Dysglycemia appears to be directly linked to risk, with HbA1c concentrations powerfully predicting incident HF. Those with HbA1c >10.5% had a nearly 4-fold increase in the risk for HF compared with those with a value of <6.5%.[322] Current consensus advocates that clinicians should make every effort to control hyperglycemia, although such control has not yet been shown to reduce the subsequent risk of HF. Additionally, standard therapies for diabetes mellitus, such as use of ACE inhibitors or ARBs, can prevent the development of other risk factors for HF, such as renal dysfunction,[325,326] and may themselves directly lower the likelihood of HF.[327–329] Although risk models for the development of incident HF in patients with diabetes mellitus have been developed,[323] their prospective use to reduce risk has not been validated. Despite the lack of supportive, prospective, randomized data, consensus exists that risk factor recognition and modification are vital for the prevention of HF among at-risk patients (eg, obese patients or patients with diabetes mellitus).

7.1.4. Recognition and Control of Other Conditions That May Lead to HF

A substantial genetic risk exists in some patients for the development of HF. As noted in Section 6.1, obtaining a 3-generation family history of HF is recommended. Adequate therapy of AF is advisable, given a clear association between uncontrolled heart rate and development of HF. Many therapeutic agents can exert important cardiotoxic effects, with consequent risk for HF, and clinicians should be aware of such risk. For example, cardiotoxic chemotherapy regimens (particularly anthracycline based) and trastuzumab may increase the risk for HF in certain patients[330–332]; it may be reasonable to evaluate those who are receiving (or who have received) such agents for LV dysfunction. The use of advanced echocardiographic techniques or biomarkers to identify increased HF risk in those receiving chemotherapy may be useful but remain unvalidated as yet.[333]

Tobacco use is strongly associated with risk for incident HF,[92,320,334] and patients should be strongly advised about the hazards of smoking, with attendant efforts at quitting. Cocaine and amphetamines are anecdotally but strongly associated with HF, and their avoidance is mandatory. Although it is recognized that alcohol consumption is associated with subsequent

development of HF,[92,139,140] there is some uncertainty about the amount of alcohol ingested and the likelihood of developing HF, and there may be sex differences as well. Nevertheless, the heavy use of alcohol has repeatedly been associated with heightened risk for development of HF. Therefore, patients should be counseled about their alcohol intake.

Although several epidemiological studies have revealed an independent link between risk for incident HF and biomarkers such as natriuretic peptides,[335,336] highly sensitive troponin,[337] and measures of renal function such as creatinine, phosphorus, urinary albumin, or albumin-creatinine ratio,[320,323,334,336,338–340] it remains unclear whether the risk for HF reflected by any of these biomarkers is modifiable. Although routine screening with BNP before echocardiography may be a cost-effective strategy to identify high-risk patients,[341] routine measurement of biomarkers in stage A patients is not yet justified.

See Online Data Supplement 11 for additional data on stage A HF.

7.2. Stage B: Recommendations

See Table 12 for a summary of recommendations from this section.

Class I

1. **In all patients with a recent or remote history of MI or ACS and reduced EF, ACE inhibitors should be used to prevent symptomatic HF and reduce mortality.[342–344] In patients intolerant of ACE inhibitors, ARBs are appropriate unless contraindicated.[314,345] *(Level of Evidence: A)***
2. **In all patients with a recent or remote history of MI or ACS and reduced EF, evidence-based beta blockers should be used to reduce mortality.[346–348] *(Level of Evidence: B)***
3. **In all patients with a recent or remote history of MI or ACS, statins should be used to prevent symptomatic HF and cardiovascular events.[104,349–354] *(Level of Evidence: A)***
4. **In patients with structural cardiac abnormalities, including LV hypertrophy, in the absence of a history of MI or ACS, blood pressure should be controlled in accordance with clinical practice guidelines for hypertension to prevent symptomatic HF.[27,94,311–313] *(Level of Evidence: A)***
5. **ACE inhibitors should be used in all patients with a reduced EF to prevent symptomatic HF, even if they do not have a history of MI.[65,344] *(Level of Evidence: A)***
6. **Beta blockers should be used in all patients with a reduced EF to prevent symptomatic HF, even if they do not have a history of MI. *(Level of Evidence: C)***

Class IIa

1. **To prevent sudden death, placement of an ICD is reasonable in patients with asymptomatic ischemic cardiomyopathy who are at least 40 days post-MI, have an LVEF of 30% or less, are on appropriate medical therapy, and have reasonable expectation of survival with a good functional status for more than 1 year.[355] *(Level of Evidence: B)***

Class III: Harm

1. **Nondihydropyridine calcium channel blockers with negative inotropic effects may be harmful in asymptomatic patients with low LVEF and no symptoms of HF after MI. *(Level of Evidence: C)***

Patients with reduced LVEF may not have HF symptoms and are most often identified during an evaluation for another disorder (eg, abnormal heart sounds, abnormal ECG, abnormal chest x-ray, hypertension or hypotension, an arrhythmia, acute MI, or pulmonary or systemic thromboembolic event). However, the cost-effectiveness of routine periodic population screening for asymptomatic reduced LVEF is not recommended at this time. Echocardiographic evaluation should be performed in selected patients who are at high risk of reduced LVEF (eg, those with a strong family history of cardiomyopathy, long-standing

Table 12. Recommendations for Treatment of Stage B HF

Recommendations	COR	LOE	References
In patients with a history of MI and reduced EF, ACE inhibitors or ARBs should be used to prevent HF	I	A	314, 342–345
In patients with MI and reduced EF, evidence-based beta blockers should be used to prevent HF	I	B	346–348
In patients with MI, statins should be used to prevent HF	I	A	104, 349–354
Blood pressure should be controlled to prevent symptomatic HF	I	A	27, 94, 311–313
ACE inhibitors should be used in all patients with a reduced EF to prevent HF	I	A	65, 344
Beta blockers should be used in all patients with a reduced EF to prevent HF	I	C	N/A
An ICD is reasonable in patients with asymptomatic ischemic cardiomyopathy who are at least 40 d post-MI, have an LVEF ≤30%, and on GDMT	IIa	B	355
Nondihydropyridine calcium channel blockers may be harmful in patients with low LVEF	III: Harm	C	N/A

ACE indicates angiotensin-converting enzyme; ARB, angiotensin-receptor blocker; COR, Class of Recommendation; EF, ejection fraction; GDMT, guideline-directed medical therapy; HF, heart failure; ICD, implantable cardioverter-defibrillator; LOE, Level of Evidence; LVEF, left ventricular ejection fraction; MI, myocardial infarction; and N/A, not available.

hypertension, previous MI, or those receiving cardiotoxic therapies). In addition, it should be acknowledged that many adults may have asymptomatic valvular abnormalities or congenital heart lesions that if unrecognized could lead to the development of clinical HF. Although these asymptomatic patients are in stage B as well, the management of valvular and congenital heart disease is beyond the scope of this guideline.

7.2.1. Management Strategies for Stage B

In general, all recommendations for patients with stage A HF also apply to those with stage B HF, particularly with respect to control of blood pressure in the patient with LV hypertrophy[27,94,311,312] and the optimization of lipids with statins.[349,356] CAD is a major risk factor for the development of HF and a key target for prevention of HF. The 5-year risk of developing HF after acute MI is 7% and 12% for men and women, respectively; for men and women between the ages of 40 and 69 and those >70 years of age, the risk is 22% and 25%, respectively.[51] Current evidence supports the use of ACE inhibitors and (to a lower level of evidence) beta-blocker therapy to impede maladaptive LV remodeling in patients with stage B HF and low LVEF to improve mortality and morbidity.[344] At 3-year follow-up, those patients treated with ACE inhibitors demonstrated combined endpoints of reduced hospitalization or death, a benefit that extended up to a 12-year follow-up.[65] ARBs are reasonable alternatives to ACE inhibitors. In 1 study, losartan reduced adverse outcomes in a population with hypertension,[357] and in another study of patients post-MI with low LVEF, valsartan was equivalent to captopril.[345] Data with beta blockers are less convincing in a population with known CAD, although in 1 trial[346] carvedilol therapy in patients with stage B and low LVEF was associated with a 31% relative risk reduction in adverse long-term outcomes. In patients with previously established structural heart disease, the administration of agents known to have negative inotropic properties such as nondihydropyridine calcium channel blockers and certain antiarrhythmics should be avoided.

Elevations in both systolic and diastolic blood pressure are major risk factors for developing LV hypertrophy, another form of stage B.[91,92] Although the magnitude of benefit varies with the trial selection criteria, target blood pressure reduction, and HF criteria, effective hypertension treatment invariably reduces HF events. Consequently, long-term treatment of both systolic and diastolic hypertension reduces the risk of moving from stage A or B to stage C HF.[93,94,311,329] Several large controlled studies have uniformly demonstrated that optimal blood pressure control decreases the risk of new HF by approximately 50%.[96] It is imperative that strategies to control hypertension be part of any effort to prevent HF.

Clinicians should lower both systolic and diastolic blood pressure in accordance with published guidelines.[27] Target levels of blood pressure lowering depend on major cardiovascular risk factors, (eg, CAD, diabetes mellitus, or renal disease).[358] Thus, when an antihypertensive regimen is devised, optimal control of blood pressure should remain the primary goal, with the choice of drugs determined by the concomitant medical problems.

Diuretic-based antihypertensive therapy has been shown to prevent HF in a wide range of target populations.[359,360] In refractory hypertensive patients, spironolactone (25 mg) should be considered as an additional agent.[27] Eplerenone, in synergy with enalapril, has also demonstrated reduction in LV mass.[361]

Table 13. Other ACCF/AHA Guidelines Addressing Patients With Stage B HF

Consideration	Reference
Patients with an acute MI who have not developed HF symptoms treated according to GDMT	2013 UA/NSTEMI Guideline[16] 2013 STEMI Guideline[15]
Coronary revascularization for patients without symptoms of HF in accordance with GDMT	2011 PCI Guideline[12] 2011 CABG Guideline[10] 2012 SIHD Guideline[14]
Valve replacement or repair for patients with hemodynamically significant valvular stenosis or regurgitation and no symptoms of HF in accordance with GDMT	2008 Focused Update incorporated into the 2006 VHD Guideline[17]

ACCF indicates American College of Cardiology Foundation; AHA, American Heart Association; CABG, coronary artery bypass graft; GDMT, guideline-directed medical therapy; HF, heart failure; MI, myocardial infarction; PCI, percutaneous coronary intervention; SIHD, stable ischemic heart disease; STEMI, ST-elevation myocardial infarction; UA/NSTEMI, unstable angina/non–ST-elevation myocardial infarction; and VHD, valvular heart disease.

ACE inhibitors and beta blockers are also effective in the prevention of HF.[27] Nevertheless, neither ACE inhibitors nor beta blockers as single therapies are superior to other antihypertensive drug classes, including calcium channel blockers, in the reduction of all cardiovascular outcomes. However, in patients with type 2 diabetes mellitus, ACE inhibitors and ARBs significantly reduced the incidence of HF in patients.[327–329] In contrast, calcium channel blockers and alpha blockers were less effective in preventing the HF syndrome, particularly in HF*r*EF.[359]

The Framingham studies have shown a 60% increased risk of death in patients with asymptomatic low LVEF compared with those with normal LVEF; almost half of these patients remained free of HF before their death.[62–65] MADIT-II (Multicenter Automatic Defibrillator Implantation Trial II)[362] demonstrated a 31% relative risk reduction in all-cause mortality in patients with post-MI with LVEF ≤30% receiving a prophylactic ICD compared with standard of care.[355] These findings provided justification for broad adoption of ICDs for primary prevention of SCD in the post-MI setting with reduced LVEF, even in the absence of HF symptoms, that is, patients in stage B HF.

Several other ACCF/AHA guidelines addressing the appropriate management of patients with stage B—those with cardiac structural abnormalities but no symptoms of HF—are listed in Table 13.

See Online Data Supplement 12 for additional data on stage B HF.

7.3. Stage C

See Online Data Supplement 13 for additional data on stage C HF.

7.3.1. Nonpharmacological Interventions

7.3.1.1. Education: Recommendation

Class I

1. **Patients with HF should receive specific education to facilitate HF self-care.[363–368] *(Level of Evidence: B)***

The self-care regimen for patients with HF is complex and multifaceted.[363] Patients need to understand how to monitor their symptoms and weight fluctuations, restrict their sodium

intake, take their medications as prescribed, and stay physically active. Education regarding these recommendations is necessary, albeit not always sufficient, to significantly improve outcomes. After discharge, many patients with HF need disease management programs, which are reviewed in Section 11.

A systematic review of 35 educational intervention studies for patients with HF demonstrated that education improved knowledge, self-monitoring, medication adherence, time to hospitalization, and days in the hospital.[363] Patients who receive in-hospital education have higher knowledge scores at discharge and 1 year later when compared with those who did not receive in-hospital education.[364] Data have called into question the survival benefit of discharge education.[369,370] However, prior data have suggested that discharge education may result in fewer days of hospitalization, lower costs, and lower mortality rates within a 6-month follow-up.[365] Patients educated in all 6 categories of the HF core measures from The Joint Commission were significantly less likely to be readmitted for any cause, including HF.[366] Even a single home-based educational intervention for patients and families has been shown to decrease emergency visits and unplanned hospitalizations in adults with HF.[367]

See Online Data Supplement 14 for additional data on patient nonadherence.

7.3.1.2. Social Support

Social support is thought to buffer stress and promote treatment adherence and a healthy lifestyle.[371] Most studies examining the relationship between social support and hospitalization in adults with HF have found that a lack of social support is associated with higher hospitalization rates [372,373] and mortality risk.[374,375]

7.3.1.3. Sodium Restriction: Recommendation

Class IIa

1. **Sodium restriction is reasonable for patients with symptomatic HF to reduce congestive symptoms. *(Level of Evidence: C)***

Dietary sodium restriction is commonly recommended to patients with HF and is endorsed by many guidelines.[18,376,377] The data on which this recommendation is drawn upon, however, are modest, and variances in protocols, fluid intake, measurement of sodium intake and compliance, and other clinical and therapeutic characteristics among these studies make it challenging to compare data and draw definitive conclusions. Observational data suggest an association between dietary sodium intake with fluid retention and risk for hospitalization.[378,379] Other studies, however, have signaled a worsening neurohormonal profile with sodium restriction in HF.[380–390] Sodium homeostasis is altered in patients with HF as opposed to healthy individuals, which may partially explain these trends. In most of these studies, patients were not receiving GDMT; no study to date has evaluated the effects of sodium restriction on neurohormonal activation and outcomes in optimally treated patients with HF. With the exception of 1 observational study that evaluated patients with HF*p*EF,[383] all other studies have focused on patients with HF*r*EF. These data are mostly from white patients; when the differences in cardiovascular and renal pathophysiology among races are considered, the effects of sodium restriction in nonwhite patients with HF cannot be ascertained from these studies. To make this more complicated, the 3 RCTs that assessed outcomes with sodium restriction have all shown that lower sodium intake is associated with worse outcomes in patients with HF*r*EF.[384–386]

These limitations make it difficult to give precise recommendations about daily sodium intake and whether it should vary with respect to the type of HF (eg, HF*r*EF versus HF*p*EF), disease severity (eg, NYHA class), HF-related comorbidities (eg, renal dysfunction), or other characteristics (eg, age or race). Because of the association between sodium intake and hypertension, LV hypertrophy, and cardiovascular disease, the AHA recommendation for restriction of sodium to 1500 mg/d appears to be appropriate for most patients with stage A and B HF.[387–392] However, for patients with stage C and D HF, currently there are insufficient data to endorse any specific level of sodium intake. Because sodium intake is typically high (>4 g/d) in the general population, clinicians should consider some degree (eg, <3 g/d) of sodium restriction in patients with stage C and D HF for symptom improvement.

7.3.1.4. Treatment of Sleep Disorders: Recommendation

Class IIa

1. **Continuous positive airway pressure can be beneficial to increase LVEF and improve functional status in patients with HF and sleep apnea.[393–396] *(Level of Evidence: B)***

Sleep disorders are common in patients with HF. A study of adults with chronic HF treated with evidence-based therapies found that 61% had either central or obstructive sleep apnea.[397] Despite having less sleep time and sleep efficiency compared with those without HF, patients with HF, including those with documented sleep disorders, rarely report excessive daytime sleepiness.[398] Thus, a high degree of suspicion for sleep disorders should be maintained for these patients. The decision to refer a patient to a sleep study should be based on clinical judgment.

The primary treatment for obstructive sleep apnea is nocturnal continuous positive airway pressure. In a major trial, continuous positive airway pressure for obstructive sleep apnea was effective in decreasing the apnea–hypopnea index, improving nocturnal oxygenation, increasing LVEF, lowering norepinephrine levels, and increasing the distance walked in 6 minutes; these benefits were sustained for up to 2 years.[394] Smaller studies suggest that continuous positive airway pressure can improve cardiac function, sympathetic activity, and HRQOL in patients with HF and obstructive sleep apnea.[395,396]

See Online Data Supplement 15 for additional data on the treatment of sleep disorders.

7.3.1.5. Weight Loss

Obesity is defined as a BMI ≥30 kg/m^2. Patients with HF who have a BMI between 30 and 35 kg/m^2 have lower mortality and hospitalization rates than those with a BMI in the normal range.[99] Weight loss may reflect cachexia caused by the higher total energy expenditure associated with HF compared with that of healthy sedentary subjects.[399] The diagnosis of cardiac cachexia independently predicts a worse prognosis.[191] At the other end of the continuum, morbidly obese patients may have worse outcomes compared with patients within the normal weight range and those who are obese. A U-shaped distribution curve has been suggested in which mortality is greatest in cachectic

patients; lower in normal, overweight, and mildly obese patients; and higher again in more severely obese patients.[400]

Although there are anecdotal reports about symptomatic improvement after weight reduction in obese patients with HF,[401,402] large-scale clinical trials on the role of weight loss in patients with HF with obesity have not been performed. Because of reports of development of cardiomyopathy, sibutramine is contraindicated in HF.[403]

7.3.1.6. Activity, Exercise Prescription, and Cardiac Rehabilitation: Recommendations

Class I

1. **Exercise training (or regular physical activity) is recommended as safe and effective for patients with HF who are able to participate to improve functional status.[404–407] *(Level of Evidence: A)***

Class IIa

1. **Cardiac rehabilitation can be useful in clinically stable patients with HF to improve functional capacity, exercise duration, HRQOL, and mortality.[404,406–411] *(Level of Evidence: B)***

Exercise training in patients with HF is safe and has numerous benefits. Meta-analyses show that cardiac rehabilitation reduces mortality; improves functional capacity, exercise duration, and HRQOL; and reduces hospitalizations.[409] Other benefits include improved endothelial function, blunted catecholamine spillover, increased peripheral oxygen extraction, and reduced hospital admission.[405,407,410,411]

Many RCTs of exercise training in HF have been conducted, but the statistical power of most was low.[408] A major trial of exercise and HF randomly assigned 2331 patients (mean EF, 25%; ischemic etiology, 52%) to either exercise training for 3 months or usual care.[406] In unadjusted analyses, there was no significant difference at the end of the study in either total mortality or hospitalizations. When adjusted for coronary heart disease risk factors, there was an 11% reduction in all-cause mortality, cardiovascular disease mortality, or hospitalizations ($P<0.03$) in the exercise training group.[406] A meta-analysis demonstrated improved peak oxygen consumption and decreased all-cause mortality with exercise.[409]

See Online Data Supplement 16 for additional data on cardiac exercise.

7.3.2. Pharmacological Treatment for Stage C HFrEF: Recommendations

Class I

1. **Measures listed as Class I recommendations for patients in stages A and B are recommended where appropriate for patients in stage C. *(Levels of Evidence: A, B, and C as appropriate)***
2. **GDMT as depicted in Figure 1 should be the mainstay of pharmacological therapy for HF*r*EF.[108,343,345,346,412–426] *(Level of Evidence: A)***

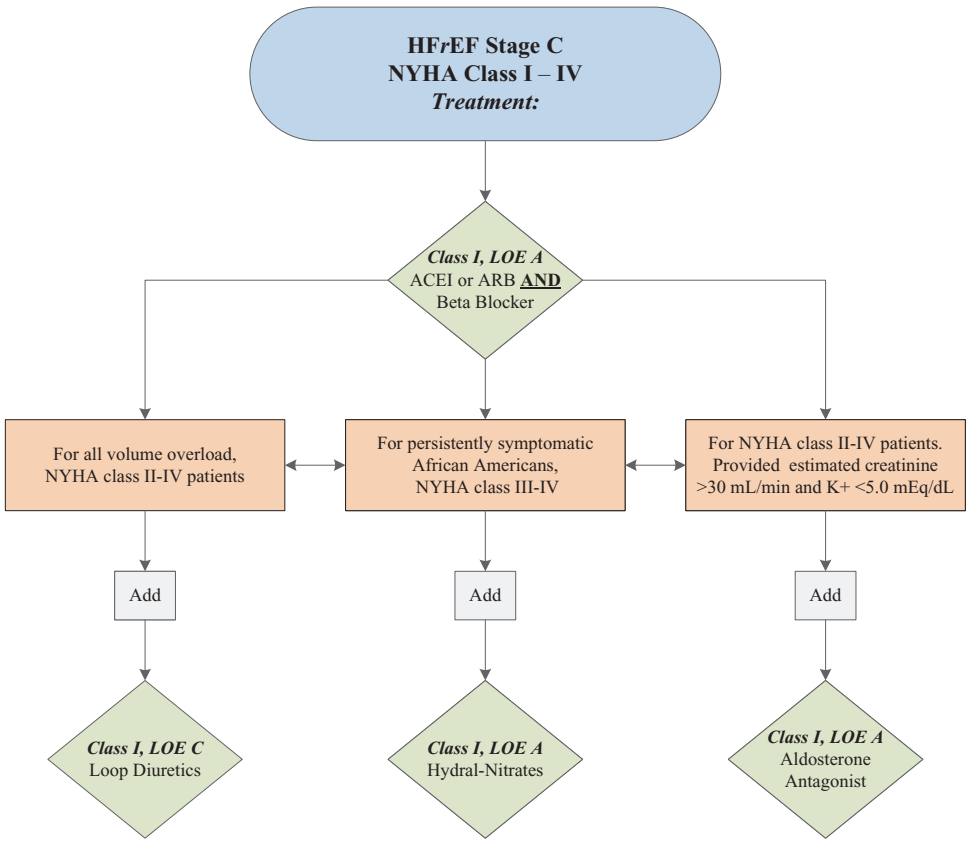


Figure 1. Stage C HF*r*EF: evidence-based, guideline-directed medical therapy. ACEI indicates angiotensin-converting enzyme inhibitor; ARB, angiotensin-receptor blocker; HF*r*EF, heart failure with reduced ejection fraction; Hydral-Nitrates, hydralazine and isosorbide dinitrate; LOE, Level of Evidence; and NYHA, New York Heart Association.

7.3.2.1. Diuretics: Recommendation

Class I

1. **Diuretics are recommended in patients with HF*r*EF who have evidence of fluid retention, unless contraindicated, to improve symptoms. *(Level of Evidence: C)***

Diuretics inhibit the reabsorption of sodium or chloride at specific sites in the renal tubules. Bumetanide, furosemide, and torsemide act at the loop of Henle (thus, the term loop diuretics), whereas thiazides, metolazone, and potassium-sparing agents (eg, spironolactone) act in the distal portion of the tubule.[427,428] Loop diuretics have emerged as the preferred diuretic agents for use in most patients with HF. Thiazide diuretics may be considered in hypertensive patients with HF and mild fluid retention because they confer more persistent antihypertensive effects.

Controlled trials have demonstrated the ability of diuretic drugs to increase urinary sodium excretion and decrease physical signs of fluid retention in patients with HF.[429,430] In intermediate-term studies, diuretics have been shown to improve symptoms and exercise tolerance in patients with HF[431–433]; however, diuretic effects on morbidity and mortality are not known. Diuretics are the only drugs used for the treatment of HF that can adequately control the fluid retention of HF. Appropriate use of diuretics is a key element in the success of other drugs used for the treatment of HF. The use of inappropriately low doses of diuretics will result in fluid retention. Conversely, the use of inappropriately high doses of diuretics will lead to volume contraction, which can increase the risk of hypotension and renal insufficiency.

7.3.2.1.1. Diuretics: Selection of Patients. Diuretics should be prescribed to all patients who have evidence of, and to most patients with a prior history of, fluid retention. Diuretics should generally be combined with an ACE inhibitor, beta blocker, and aldosterone antagonist. Few patients with HF will be able to maintain target weight without the use of diuretics.

7.3.2.1.2. Diuretics: Initiation and Maintenance. The most commonly used loop diuretic for the treatment of HF is furosemide, but some patients respond more favorably to other agents in this category (eg, bumetanide, torsemide) because of their increased oral bioavailability.[434,435] Table 14 lists oral diuretics recommended for use in the treatment of chronic HF. In outpatients with HF, diuretic therapy is commonly initiated with low doses, and the dose is increased until urine output increases and weight decreases, generally by 0.5 to 1.0 kg daily. Further increases in the dose or frequency (ie, twice-daily dosing) of diuretic administration may be required to maintain an active diuresis and sustain weight loss. The ultimate goal of diuretic treatment is to eliminate clinical evidence of fluid retention. Diuretics are generally combined with moderate dietary sodium restriction. Once fluid retention has resolved, treatment with the diuretic should be maintained in some patients to prevent the recurrence of volume overload. Patients are commonly prescribed a fixed dose of diuretic, but the dose of these drugs frequently may need adjustment. In many cases, this adjustment can be accomplished by having patients record their weight each day and adjusting the diuretic dosage if weight increases or decreases beyond a specified range. Patients may become unresponsive to high doses of diuretic drugs if they consume large amounts of dietary sodium, are taking agents that can block the effects of diuretics (eg, nonsteroidal anti-inflammatory drugs [NSAIDs], including cyclooxygenase-2 inhibitors)[436–438] or have a significant impairment of renal function or perfusion.[434] Diuretic resistance can generally be overcome by the intravenous administration of diuretics (including the use of continuous infusions)[439] or combination of different diuretic classes (eg, metolazone with a loop diuretic).[440–443]

Table 14. Oral Diuretics Recommended for Use in the Treatment of Chronic HF

Drug	Initial Daily Dose(s)	Maximum Total Daily Dose	Duration of Action
Loop diuretics			
Bumetanide	0.5 to 1.0 mg once or twice	10 mg	4 to 6 h
Furosemide	20 to 40 mg once or twice	600 mg	6 to 8 h
Torsemide	10 to 20 mg once	200 mg	12 to 16 h
Thiazide diuretics			
Chlorothiazide	250 to 500 mg once or twice	1000 mg	6 to 12 h
Chlorthalidone	12.5 to 25.0 mg once	100 mg	24 to 72 h
Hydrochlorothiazide	25 mg once or twice	200 mg	6 to 12 h
Indapamide	2.5 mg once	5 mg	36 h
Metolazone	2.5 mg once	20 mg	12 to 24 h
Potassium-sparing diuretics*			
Amiloride	5 mg once	20 mg	24 h
Spironolactone	12.5 to 25.0 mg once	50 mg†	1 to 3 h
Triamterene	50 to 75 mg twice	200 mg	7 to 9 h
Sequential nephron blockade			
Metolazone‡	2.5 to 10.0 mg once plus loop diuretic	N/A	N/A
Hydrochlorothiazide	25 to 100 mg once or twice plus loop diuretic	N/A	N/A
Chlorothiazide (IV)	500 to 1000 mg once plus loop diuretic	N/A	N/A

*Eplerenone, although also a diuretic, is primarily used in chronic HF.
†Higher doses may occasionally be used with close monitoring.
‡See Section 8.4.
HF indicates heart failure; IV, intravenous; and N/A, not applicable.

7.3.2.1.3. Diuretics: Risks of Treatment. The principal adverse effects of diuretics include electrolyte and fluid depletion, as well as hypotension and azotemia. Diuretics can cause the depletion of potassium and magnesium, which can predispose patients to serious cardiac arrhythmias.[444] The risk of electrolyte depletion is markedly enhanced when 2 diuretics are used in combination.

See Online Data Supplement 17 for additional data on diuretics.

7.3.2.2. ACE Inhibitors: Recommendation

Class I

1. **ACE inhibitors are recommended in patients with HF*r*EF and current or prior symptoms, unless**

contraindicated, to reduce morbidity and mortality.[343,412–414] *(Level of Evidence: A)*

7.3.2.2.1. ACE Inhibitors: Selection of Patients. ACE inhibitors can reduce the risk of death and reduce hospitalization in HF*r*EF. The benefits of ACE inhibition were seen in patients with mild, moderate, or severe symptoms of HF and in patients with or without CAD. ACE inhibitors should be prescribed to all patients with HF*r*EF. Unless there is a contraindication, ACE inhibitors are used together with a beta blocker. Patients should not be given an ACE inhibitor if they have experienced life-threatening adverse reactions (ie, angioedema) during previous medication exposure or if they are pregnant or plan to become pregnant. Clinicians should prescribe an ACE inhibitor with caution if the patient has very low systemic blood pressures (systolic blood pressure <80 mm Hg), markedly increased serum levels of creatinine (>3 mg/dL), bilateral renal artery stenosis, or elevated levels of serum potassium (>5.0 mEq/L).

7.3.2.2.2. ACE Inhibitors: Initiation and Maintenance. The available data suggest that there are no differences among available ACE inhibitors in their effects on symptoms or survival.[414] Treatment with an ACE inhibitor should be initiated at low doses (Table 15), followed by gradual dose increments if lower doses have been well tolerated. Renal function and serum potassium should be assessed within 1 to 2 weeks of initiation of therapy and periodically thereafter, especially in patients with preexisting hypotension, hyponatremia, diabetes mellitus, azotemia, or in those taking potassium supplements. In controlled clinical trials that were designed to evaluate survival, the dose of the ACE inhibitor was not determined by a patient's therapeutic response but was increased until the predetermined target dose was reached.[343,413,414] Clinicians should attempt to use doses that have been shown to reduce the risk of cardiovascular events in clinical trials. If these target doses of an ACE inhibitor cannot be used or are poorly tolerated, intermediate doses should be used with the expectation that there are likely to be only small differences in efficacy between low and high doses. Abrupt withdrawal of treatment with an ACE inhibitor can lead to clinical deterioration and should be avoided.

Table 15. Drugs Commonly Used for Stage C HF*r*EF

Drug	Initial Daily Dose(s)	Maximum Dose(s)	Mean Doses Achieved in Clinical Trials
ACE inhibitors			
Captopril	6.25 mg 3 times	50 mg 3 times	122.7 mg/d[422]
Enalapril	2.5 mg twice	10 to 20 mg twice	16.6 mg/d[413]
Fosinopril	5 to 10 mg once	40 mg once	N/A
Lisinopril	2.5 to 5 mg once	20 to 40 mg once	32.5 to 35.0 mg/d[445]
Perindopril	2 mg once	8 to 16 mg once	N/A
Quinapril	5 mg twice	20 mg twice	N/A
Ramipril	1.25 to 2.5 mg once	10 mg once	N/A
Trandolapril	1 mg once	4 mg once	N/A
ARBs			
Candesartan	4 to 8 mg once	32 mg once	24 mg/d[420]
Losartan	25 to 50 mg once	50 to 150 mg once	129 mg/d[421]
Valsartan	20 to 40 mg twice	160 mg twice	254 mg/d[108]
Aldosterone antagonists			
Spironolactone	12.5 to 25.0 mg once	25 mg once or twice	26 mg/d[425]
Eplerenone	25 mg once	50 mg once	42.6 mg/d[446]
Beta blockers			
Bisoprolol	1.25 mg once	10 mg once	8.6 mg/d[117]
Carvedilol	3.125 mg twice	50 mg twice	37 mg/d[447]
Carvedilol CR	10 mg once	80 mg once	N/A
Metoprolol succinate extended release (metoprolol CR/XL)	12.5 to 25 mg once	200 mg once	159 mg/d[448]
Hydralazine and isosorbide dinitrate			
Fixed-dose combination[424]	37.5 mg hydralazine/20 mg isosorbide dinitrate 3 times daily	75 mg hydralazine/40 mg isosorbide dinitrate 3 times daily	~175 mg hydralazine/90 mg isosorbide dinitrate daily
Hydralazine and isosorbide dinitrate[449]	Hydralazine: 25 to 50 mg, 3 or 4 times daily and isosorbide dinitrate: 20 to 30 mg 3 or 4 times daily	Hydralazine: 300 mg daily in divided doses and isosorbide dinitrate: 120 mg daily in divided doses	N/A

ACE indicates angiotensin-converting enzyme; ARB, angiotensin-receptor blocker; CR, controlled release; CR/XL, controlled release/extended release; HF*r*EF, heart failure with reduced ejection fraction; and N/A, not applicable.

7.3.2.2.3. ACE Inhibitors: Risks of Treatment. The majority of the adverse reactions of ACE inhibitors can be attributed to the 2 principal pharmacological actions of these drugs: those related to angiotensin suppression and those related to kinin potentiation. Other types of adverse effects may also occur (eg, rash and taste disturbances). Up to 20% of patients will experience an ACE inhibitor–induced cough. With the use of ACE inhibitors, particular care should be given to the patient's volume status, renal function, and concomitant medications (Sections 7.3.2.1 and 7.3.2.9). However, most HF patients (85% to 90%) can tolerate these drugs.

See Online Data Supplement 18 for additional data on ACE inhibitors.

7.3.2.3. ARBs: Recommendations

Class I

1. **ARBs are recommended in patients with HF*r*EF with current or prior symptoms who are ACE inhibitor intolerant, unless contraindicated, to reduce morbidity and mortality.[108,345,415,450] *(Level of Evidence: A)***

Class IIa

1. **ARBs are reasonable to reduce morbidity and mortality as alternatives to ACE inhibitors as first-line therapy for patients with HF*r*EF, especially for patients already taking ARBs for other indications, unless contraindicated.[451–456] *(Level of Evidence: A)***

Class IIb

1. **Addition of an ARB may be considered in persistently symptomatic patients with HF*r*EF who are already being treated with an ACE inhibitor and a beta blocker in whom an aldosterone antagonist is not indicated or tolerated.[420,457] *(Level of Evidence: A)***

Class III: Harm

1. **Routine *combined* use of an ACE inhibitor, ARB, and aldosterone antagonist is potentially harmful for patients with HF*r*EF. *(Level of Evidence: C)***

ARBs were developed with the rationale that a) angiotensin II production continues in the presence of ACE inhibition, driven through alternative enzyme pathways and b) interference with the renin-angiotensin system without inhibition of kininase would produce all of the benefits of ACE inhibitors while minimizing the risk of adverse reactions to them. However, it is now known that some of the benefits of ACE inhibitors may be related to the accumulation of kinins rather than to the suppression of angiotensin II formation, whereas some of the adverse effects of ACE inhibitors in HF are related to the suppression of angiotensin II formation.

In several placebo-controlled studies, long-term therapy with ARBs produced hemodynamic, neurohormonal, and clinical effects consistent with those expected after interference with the renin-angiotensin system. Reduced hospitalization and mortality have been demonstrated. ACE inhibitors remain the first choice for inhibition of the renin-angiotensin system in systolic HF, but ARBs can now be considered a reasonable alternative.

7.3.2.3.1. ARBs: Selection of Patients. ARBs are used in patients with HF*r*EF who are ACE inhibitor intolerant; an ACE-inhibition intolerance primarily related to cough is the most common indication. In addition, an ARB may be used as an alternative to an ACE inhibitor in patients who are already taking an ARB for another reason, such as hypertension, and who subsequently develop HF. Angioedema occurs in <1% of patients who take an ACE inhibitor, but it occurs more frequently in blacks. Because its occurrence may be life-threatening, clinical suspicion of this reaction justifies the subsequent avoidance of all ACE inhibitors for the lifetime of the patient. ACE inhibitors should not be initiated in any patient with a history of angioedema. Although ARBs may be considered as alternative therapy for patients who have developed angioedema while taking an ACE inhibitor, there are some patients who have also developed angioedema with ARBs, and caution is advised when substituting an ARB in a patient who has had angioedema associated with use of an ACE inhibitor.[458–461]

7.3.2.3.2. ARBs: Initiation and Maintenance. When used, ARBs should be initiated with the starting doses shown in Table 15. Many of the considerations with initiation of an ARB are similar to those with initiation of an ACE inhibitor, as discussed previously. Blood pressure (including postural blood pressure changes), renal function, and potassium should be reassessed within 1 to 2 weeks after initiation and followed closely after changes in dose. Patients with systolic blood pressure <80 mm Hg, low serum sodium, diabetes mellitus, and impaired renal function merit close surveillance during therapy with inhibitors of the renin angiotensin-aldosterone system. Titration is generally achieved by doubling doses. For stable patients, it is reasonable to add therapy with beta-blocking agents before full target doses of either ACE inhibitors or ARBs are reached.

7.3.2.3.3. ARBs: Risks of Treatment. The risks of ARBs are attributed to suppression of angiotensin stimulation. These risks of hypotension, renal dysfunction, and hyperkalemia are greater when combined with another inhibitor of this neurohormonal axis, such as ACE inhibitors or aldosterone antagonists.

See Online Data Supplement 19 for additional data on ARBs.

7.3.2.4. Beta Blockers: Recommendation

Class I

1. **Use of 1 of the 3 beta blockers proven to reduce mortality (eg, bisoprolol, carvedilol, and sustained-release metoprolol succinate) is recommended for all patients with current or prior symptoms of HF*r*EF, unless contraindicated, to reduce morbidity and mortality.[346,416–419,448] *(Level of Evidence: A)***

Long-term treatment with beta blockers can lessen the symptoms of HF, improve the patient's clinical status, and enhance the patient's overall sense of well-being.[462–469] In addition, like ACE inhibitors, beta blockers can reduce the risk of death and the combined risk of death or hospitalization.[117,447,448,470,471] These benefits of beta blockers were seen in patients with or without CAD and in patients with or without diabetes mellitus, as well as in women and blacks. The favorable effects

of beta blockers were also observed in patients already taking ACE inhibitors.

Three beta blockers have been shown to be effective in reducing the risk of death in patients with chronic HF*r*EF: bisoprolol and sustained-release metoprolol (succinate), which selectively block beta-1–receptors; and carvedilol, which blocks alpha-1–, beta-1–, and beta-2–receptors. Positive findings with these 3 agents, however, should not be considered a beta-blocker class effect. Bucindolol lacked uniform effectiveness across different populations, and short-acting metoprolol tartrate was less effective in HF clinical trials. Beta-1 selective blocker nebivolol demonstrated a modest reduction in the primary endpoint of all-cause mortality or cardiovascular hospitalization but did not affect mortality alone in an elderly population that included patients with HF*p*EF.[472]

7.3.2.4.1. Beta Blockers: Selection of Patients. Beta blockers should be prescribed to all patients with stable HF*r*EF unless they have a contraindication to their use or are intolerant of these drugs. Because of its favorable effects on survival and disease progression, a clinical trial–proven beta blocker should be initiated as soon as HF*r*EF is diagnosed. Even when symptoms are mild or improve with other therapies, beta-blocker therapy is important and should not be delayed until symptoms return or disease progression is documented. Therefore, even if patients have little disability and experience seemingly minimal symptomatic benefit, they should still be treated with a beta blocker to reduce the risks of disease progression, clinical deterioration, and sudden death.[117,448,469–471]

Patients need not take high doses of ACE inhibitors before initiation of beta-blocker therapy. In patients taking a low dose of an ACE inhibitor, the addition of a beta blocker produces a greater improvement in symptoms and reduction in the risk of death than does an increase in the dose of the ACE inhibitor, even to the target doses used in clinical trials.[445,473] In patients with a current or recent history of fluid retention, beta blockers should not be prescribed without diuretics, because diuretics are needed to maintain sodium and fluid balance and prevent the exacerbation of fluid retention that can accompany the initiation of beta-blocker therapy.[474,475] Beta blockers may be considered in patients who have reactive airway disease or asymptomatic bradycardia but should be used cautiously in patients with persistent symptoms of either condition.

7.3.2.4.2. Beta Blockers: Initiation and Maintenance. Treatment with a beta blocker should be initiated at very low doses (Table 15), followed by gradual increments in dose if lower doses have been well tolerated. Patients should be monitored closely for changes in vital signs and symptoms during this uptitration period. Planned increments in the dose of a beta blocker should be delayed until any adverse effects observed with lower doses have disappeared. When such a cautious approach was used, most patients (approximately 85%) enrolled in clinical trials who received beta blockers were able to tolerate short- and long-term treatment with these drugs and achieve the maximum planned trial dose.[117,447,448,470] Data show that beta blockers can be safely started before discharge even in patients hospitalized for HF, provided they do not require intravenous inotropic therapy for HF.[476] Clinicians should make every effort to achieve the target doses of the beta blockers shown to be effective in major clinical trials. Even if symptoms do not improve, long-term treatment should be maintained to reduce the risk of major clinical events. Abrupt withdrawal of treatment with a beta blocker can lead to clinical deterioration and should be avoided.[477]

7.3.2.4.3. Beta Blockers: Risks of Treatment. Initiation of treatment with a beta blocker may produce 4 types of adverse reactions that require attention and management: fluid retention and worsening HF; fatigue; bradycardia or heart block; and hypotension. The occurrence of fluid retention or worsening HF is not generally a reason for the permanent withdrawal of treatment. Such patients generally respond favorably to intensification of conventional therapy, and once treated, they remain excellent candidates for long-term treatment with a beta blocker. The slowing of heart rate and cardiac conduction produced by beta blockers is generally asymptomatic and thus requires no treatment; however, if the bradycardia is accompanied by dizziness or lightheadedness or if second- or third-degree heart block occurs, clinicians should decrease the dose of the beta blocker. Clinicians may minimize the risk of hypotension by administering the beta blocker and ACE inhibitor at different times during the day. Hypotensive symptoms may also resolve after a decrease in the dose of diuretics in patients who are volume depleted. If hypotension is accompanied by other clinical evidence of hypoperfusion, beta-blocker therapy should be decreased or discontinued pending further patient evaluation. The symptom of fatigue is multifactorial and is perhaps the hardest symptom to address with confidence. Although fatigue may be related to beta blockers, other causes of fatigue should be considered, including sleep apnea, overdiuresis, or depression.

See Online Data Supplement 20 for additional data on beta blockers.

7.3.2.5. Aldosterone Receptor Antagonists: Recommendations

Class I

1. **Aldosterone receptor antagonists (or mineralocorticoid receptor antagonists) are recommended in patients with NYHA class II–IV HF and who have LVEF of 35% or less, unless contraindicated, to reduce morbidity and mortality. Patients with NYHA class II HF should have a history of prior cardiovascular hospitalization or elevated plasma natriuretic peptide levels to be considered for aldosterone receptor antagonists. Creatinine should be 2.5 mg/dL or less in men or 2.0 mg/dL or less in women (or estimated glomerular filtration rate >30 mL/min/1.73 m^2), and potassium should be less than 5.0 mEq/L. Careful monitoring of potassium, renal function, and diuretic dosing should be performed at initiation and closely followed thereafter to minimize risk of hyperkalemia and renal insufficiency.[425,426,478] *(Level of Evidence: A)***
2. **Aldosterone receptor antagonists are recommended to reduce morbidity and mortality following an acute MI in patients who have LVEF of 40% or less who develop symptoms of HF or who have a history of diabetes mellitus, unless contraindicated.[446] *(Level of Evidence: B)***

Table 16. Drug Dosing for Aldosterone Receptor Antagonists

	Eplerenone		Spironolactone	
eGFR (mL/min/1.73 m^2)	≥50	30 to −49	≥50	30 to 49
Initial dose (only if K^+ ≤5 mEq/L)	25 mg once daily	25 mg once every other day	12.5 to 25.0 mg once daily	12.5 mg once daily or every other day
Maintenance dose (after 4 wk for K^+ ≤5 mEq/L)*	50 mg once daily	25 mg once daily	25 mg once or twice daily	12.5 to 25.0 mg once daily

*After dose initiation for K^+, increase ≤6.0 mEq/L or worsening renal function, hold until K^+ <5.0 mEq/L. Consider restarting reduced dose after confirming resolution of hyperkalemia/renal insufficiency for at least 72 h.

eGFR indicates estimated glomerular filtration rate; and, K^+, potassium.

Adapted from Butler et al.[481]

Class III: Harm

1. **Inappropriate use of aldosterone receptor antagonists is potentially harmful because of life-threatening hyperkalemia or renal insufficiency when serum creatinine is greater than 2.5 mg/dL in men or greater than 2.0 mg/dL in women (or estimated glomerular filtration rate <30 mL/min/1.73 m^2), and/or potassium greater than 5.0 mEq/L.[479,480] *(Level of Evidence: B)***

The landmark RALES trial (Randomized Aldactone Evaluation Study)[425] showed a 30% reduction in all-cause mortality as well as a reduced risk of SCD and HF hospitalizations with the use of spironolactone in patients with chronic HF*r*EF and LVEF <35%. Eplerenone has been shown to reduce all-cause deaths, cardiovascular deaths, or HF hospitalizations in a wider range of patients with HF*r*EF.[426,446]

7.3.2.5.1. Aldosterone Receptor Antagonists: Selection of Patients. Clinicians should strongly consider the addition of the aldosterone receptor antagonists spironolactone or eplerenone for all patients with HF*r*EF who are already on ACE inhibitors (or ARBs) and beta blockers. Although the entry criteria for the trials of aldosterone receptor antagonists excluded patients with a creatinine >2.5 mg/dL, the majority of patients had much lower creatinine (95% of patients had creatinine ≤1.7 mg/dL).[425,426,446] In contrast, one third of patients in EMPHASIS-HF (Eplerenone in Mild Patients Hospitalization and Survival Study in Heart Failure) had an estimated glomerular filtration rate of <60 mL/min/1.73 m^2.[426] Note also that the entry criteria for the EMPHASIS-HF trial were age of at least ≥55 years, NYHA class II symptoms, and an EF of no more than 30% (or, if >30% to 35%, a QRS duration of >130 ms on ECG). To minimize the risk of life-threatening hyperkalemia in euvolemic patients with HF*r*EF, patients should have initial serum creatinine <2.5 mg/dL (or an estimated glomerular filtration rate >30 mL/min/1.73 m^2) without recent worsening and serum potassium <5.0 mEq/L without a history of severe hyperkalemia. Careful patient selection and risk assessment with availability of close monitoring is essential in initiating the use of aldosterone receptor antagonists.

7.3.2.5.2. Aldosterone Receptor Antagonists: Initiation and Maintenance. Spironolactone should be initiated at a dose of 12.5 to 25 mg daily, while eplerenone should be initiated at a dose of 25 mg/d, increasing to 50 mg daily. For those with concerns of hyperkalemia or marginal renal function (estimated glomerular filtration rate 30 to 49 mL/min/1.73 m^2), an initial regimen of every-other-day dosing is advised (Table 16). After initiation of aldosterone receptor antagonists, potassium supplementation should be discontinued (or reduced and carefully monitored in those with a history of hypokalemia; Table 17), and patients should be counseled to avoid foods high in potassium and NSAIDs. Potassium levels and renal function should be rechecked within 2 to 3 days and again at 7 days after initiation of an aldosterone receptor antagonist. Subsequent monitoring should be dictated by the general clinical stability of renal function and fluid status but should occur at least monthly for the first 3 months and every 3 months thereafter. The addition or an increase in dosage of ACE inhibitors or ARBs should trigger a new cycle of monitoring.

There are limited data to support or refute that spironolactone and eplerenone are interchangeable. The perceived difference between eplerenone and spironolactone is the selectivity of aldosterone receptor antagonism and not the effectiveness of blocking mineralocorticoid activity. In RALES, there was

Table 17. Strategies to Minimize the Risk of Hyperkalemia in Patients Treated With Aldosterone Antagonists

1. Impaired renal function is a risk factor for hyperkalemia during treatment with aldosterone antagonists. The risk of hyperkalemia increases progressively when serum creatinine is >1.6 mg/dL.* In elderly patients or others with low muscle mass in whom serum creatinine does not accurately reflect glomerular filtration rate, determination that glomerular filtration rate or creatinine clearance is >30 mL/min/1.73 m^2 is recommended.
2. Aldosterone antagonists would not ordinarily be initiated in patients with baseline serum potassium >5.0 mEq/L.
3. An initial dose of spironolactone of 12.5 mg or eplerenone 25 mg is typical, after which the dose may be increased to spironolactone 25 mg or eplerenone 50 mg if appropriate.
4. The risk of hyperkalemia is increased with concomitant use of higher doses of ACE inhibitors (captopril ≥75 mg daily; enalapril or lisinopril ≥10 mg daily).
5. In most circumstances, potassium supplements are discontinued or reduced when initiating aldosterone antagonists.
6. Close monitoring of serum potassium is required; potassium levels and renal function are most typically checked in 3 d and at 1 wk after initiating therapy and at least monthly for the first 3 mo.

*Although the entry criteria for the trials of aldosterone antagonists included creatinine <2.5 mg/dL, the majority of patients had much lower creatinine; in 1 trial,[425] 95% of patients had creatinine ≤1.7 mg/dL.

ACE indicates angiotensin-converting enzyme.

increased incidence (10%) of gynecomastia or breast pain with use of spironolactone (a nonselective antagonist). The incidence of these adverse events was <1% in EPHESUS (Eplerenone Post-Acute Myocardial Infarction Heart Failure Efficacy and Survival Study) and EMPHASIS-HF without any difference in adverse events between the eplerenone and placebo.[426,446]

7.3.2.5.3. Aldosterone Receptor Antagonists: Risks of Treatment. The major risk associated with use of aldosterone receptor antagonists is hyperkalemia due to inhibition of potassium excretion, ranging from 2% to 5% in large clinical trials[425,426,446] to 24% to 36% in population-based registries.[479,480] Routine triple combination of an ACE inhibitor, ARB, and aldosterone receptor antagonist should be avoided.

The development of potassium levels >5.5 mEq/L (approximately 12% in EMPHASIS-HF[426]) should generally trigger discontinuation or dose reduction of the aldosterone receptor antagonist unless other causes are identified. The development of worsening renal function should lead to careful evaluation of the entire medical regimen and consideration for stopping the aldosterone receptor antagonist. Patients should be instructed specifically to stop the aldosterone receptor antagonist during an episode of diarrhea or dehydration or while loop diuretic therapy is interrupted.

7.3.2.6. Hydralazine and Isosorbide Dinitrate: Recommendations

Class I

1. **The combination of hydralazine and isosorbide dinitrate is recommended to reduce morbidity and mortality for patients self-described as African Americans with NYHA class III–IV HF*r*EF receiving optimal therapy with ACE inhibitors and beta blockers, unless contraindicated.[423,424] *(Level of Evidence: A)***

Class IIa

1. **A combination of hydralazine and isosorbide dinitrate can be useful to reduce morbidity or mortality in patients with current or prior symptomatic HF*r*EF who cannot be given an ACE inhibitor or ARB because of drug intolerance, hypotension, or renal insufficiency, unless contraindicated.[449] *(Level of Evidence: B)***

In a large-scale trial that compared the vasodilator combination with placebo, the use of hydralazine and isosorbide dinitrate reduced mortality but not hospitalizations in patients with HF treated with digoxin and diuretics but not an ACE inhibitor or beta blocker.[449] However, in 2 other trials that compared the vasodilator combination with an ACE inhibitor, the ACE inhibitor produced more favorable effects on survival.[412,482] A post hoc retrospective analysis of these vasodilator trials demonstrated particular efficacy of isosorbide dinitrate and hydralazine in the African American cohort.[423] In a subsequent trial, which was limited to patients self-described as African American, the addition of a fixed-dose combination of hydralazine and isosorbide dinitrate to standard therapy with an ACE inhibitor or ARB, a beta blocker, and an aldosterone antagonist offered significant benefit.[424]

7.3.2.6.1. Hydralazine and Isosorbide Dinitrate: Selection of Patients. The combination of hydralazine and isosorbide dinitrate is recommended for African Americans with HF*r*EF who remain symptomatic despite concomitant use of ACE inhibitors, beta blockers, and aldosterone antagonists. Whether this benefit is evident in non–African Americans with HF*r*EF remains to be investigated. The combination of hydralazine and isosorbide dinitrate should not be used for the treatment of HF*r*EF in patients who have no prior use of standard neurohumoral antagonist therapy and should not be substituted for ACE inhibitor or ARB therapy in patients who are tolerating therapy without difficulty. Despite the lack of data with the vasodilator combination in patients who are intolerant of ACE inhibitors or ARBs, the combined use of hydralazine and isosorbide dinitrate may be considered as a therapeutic option in such patients.

7.3.2.6.2. Hydralazine and Isosorbide Dinitrate: Initiation and Maintenance. If the fixed-dose combination is available, the initial dose should be 1 tablet containing 37.5 mg of hydralazine hydrochloride and 20 mg of isosorbide dinitrate 3 times daily. The dose can be increased to 2 tablets 3 times daily for a total daily dose of 225 mg of hydralazine hydrochloride and 120 mg of isosorbide dinitrate. When the 2 drugs are used separately, both pills should be administered at least 3 times daily. Initial low doses of the drugs given separately may be progressively increased to a goal similar to that achieved in the fixed-dose combination trial.[424]

7.3.2.6.3. Hydralazine and Isosorbide Dinitrate: Risks of Treatment. Adherence to this combination has generally been poor because of the large number of tablets required, frequency of administration, and the high incidence of adverse reactions.[412,449] Frequent adverse effects include headache, dizziness, and gastrointestinal complaints. Nevertheless, the benefit of these drugs can be substantial and warrant a slower titration of the drugs to enhance tolerance of the therapy.

See Table 18 for a summary of the treatment benefit of GDMT in HF*r*EF.

Table 18. Medical Therapy for Stage C HF*r*EF: Magnitude of Benefit Demonstrated in RCTs

GDMT	RR Reduction in Mortality (%)	NNT for Mortality Reduction (Standardized to 36 mo)	RR Reduction in HF Hospitalizations (%)
ACE inhibitor or ARB	17	26	31
Beta blocker	34	9	41
Aldosterone antagonist	30	6	35
Hydralazine/nitrate	43	7	33

ACE indicates angiotensin-converting enzyme; ARB, angiotensin-receptor blocker; GDMT, guideline-directed medical therapy; HF, heart failure; HF*r*EF, heart failure with reduced ejection fraction; NNT, number needed to treat; RCTs, randomized controlled trials; and RR, relative risk.

Adapted with permission from Fonarow et al.[483]

7.3.2.7. Digoxin: Recommendation

Class IIa

1. **Digoxin can be beneficial in patients with HF*r*EF, unless contraindicated, to decrease hospitalizations for HF.[484–491] *(Level of Evidence: B)***

Several placebo-controlled trials have shown that treatment with digoxin for 1 to 3 months can improve symptoms, HRQOL, and exercise tolerance in patients with mild to moderate HF.[485–491] These benefits have been seen regardless of the underlying rhythm (normal sinus rhythm or AF), cause of HF (ischemic or nonischemic cardiomyopathy), or concomitant therapy (with or without ACE inhibitors). In a long-term trial that primarily enrolled patients with NYHA class II or III HF, treatment with digoxin for 2 to 5 years had no effect on mortality but modestly reduced the combined risk of death and hospitalization.[484]

7.3.2.7.1. Digoxin: Selection of Patients. Clinicians may consider adding digoxin in patients with persistent symptoms of HF*r*EF during GDMT. Digoxin may also be added to the initial regimen in patients with severe symptoms who have not yet responded symptomatically during GDMT.

Alternatively, treatment with digoxin may be delayed until the patient's response to GDMT has been defined and may be used only in patients who remain symptomatic despite therapy with the neurohormonal antagonists. If a patient is taking digoxin but not an ACE inhibitor or a beta blocker, treatment with digoxin should not be withdrawn, but appropriate therapy with the neurohormonal antagonists should be instituted. Digoxin is prescribed occasionally in patients with HF and AF, but beta blockers are usually more effective when added to digoxin in controlling the ventricular response, particularly during exercise.[492–495]

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

7.3.2.7.2. Digoxin: Initiation and Maintenance. Therapy with digoxin is commonly initiated and maintained at a dose of 0.125 to 0.25 mg daily. Low doses (0.125 mg daily or every other day) should be used initially if the patient is >70 years of age, has impaired renal function, or has a low lean body mass.[496] Higher doses (eg, digoxin 0.375 to 0.50 mg daily) are rarely used or needed in the management of patients with HF. There is no reason to use loading doses of digoxin to initiate therapy in patients with HF.

Doses of digoxin that achieve a plasma concentration of drug in the range of 0.5 to 0.9 ng/mL are suggested, given the limited evidence currently available. There has been no prospective, randomized evaluation of the relative efficacy or safety of different plasma concentrations of digoxin. Retrospective analysis of 2 studies of digoxin withdrawal found that prevention of worsening HF by digoxin at lower concentrations in plasma (0.5 to 0.9 ng/mL) was as great as that achieved at higher concentrations.[497,498]

7.3.2.7.3. Digoxin: Risks of Treatment. When administered with attention to dose and factors that alter its metabolism, digoxin is well tolerated by most patients with HF.[499] The principal adverse reactions occur primarily when digoxin is administered in large doses, especially in the elderly, but large doses are not necessary for clinical benefits.[500–502] The major adverse effects include cardiac arrhythmias (eg, ectopic and re-entrant cardiac rhythms and heart block), gastrointestinal symptoms (eg, anorexia, nausea, and vomiting), and neurological complaints (eg, visual disturbances, disorientation, and confusion). Overt digoxin toxicity is commonly associated with serum digoxin levels >2 ng/mL.

However, toxicity may also occur with lower digoxin levels, especially if hypokalemia, hypomagnesemia, or hypothyroidism coexists.[503,504] The concomitant use of clarithromycin, dronedarone, erythromycin, amiodarone, itraconazole, cyclosporine, propafenone, verapamil, or quinidine can increase serum digoxin concentrations and may increase the likelihood of digoxin toxicity.[505–507] The dose of digoxin should be reduced if treatment with these drugs is initiated. In addition, a low lean body mass and impaired renal function can also elevate serum digoxin levels, which may explain the increased risk of digoxin toxicity in elderly patients.

7.3.2.8. Other Drug Treatment

7.3.2.8.1. Anticoagulation: Recommendations

Class I

1. **Patients with chronic HF with permanent/persistent/paroxysmal AF and an additional risk factor for cardioembolic stroke (history of hypertension, diabetes mellitus, previous stroke or transient ischemic attack, or ≥75 years of age) should receive chronic anticoagulant therapy.*[508–514] *(Level of Evidence: A)***
2. **The selection of an anticoagulant agent (warfarin, dabigatran, apixaban, or rivaroxaban) for permanent/persistent/paroxysmal AF should be individualized on the basis of risk factors, cost, tolerability, patient preference, potential for drug interactions, and other clinical characteristics, including time in the international normalized ratio therapeutic range if the patient has been taking warfarin. *(Level of Evidence: C)***

Class IIa

1. **Chronic anticoagulation is reasonable for patients with chronic HF who have permanent/persistent/paroxysmal AF but are without an additional risk factor for cardioembolic stroke.*[509–511,515–517] *(Level of Evidence: B)***

Class III: No Benefit

1. **Anticoagulation is not recommended in patients with chronic HF*r*EF without AF, a prior thromboembolic event, or a cardioembolic source.[518–520] *(Level of Evidence: B)***

*In the absence of contraindications to anticoagulation.

Patients with chronic HF*r*EF are at an increased risk of thromboembolic events due to stasis of blood in dilated hypokinetic cardiac chambers and in peripheral blood vessels[521,522] and perhaps due to increased activity of procoagulant factors.[523] However, in large-scale studies, the risk of thromboembolism in clinically stable patients has been low (1% to 3% per year), even in those with a very depressed EF and echocardiographic evidence of intracardiac thrombi.[524–528] These rates are sufficiently low to limit the detectable benefit of anticoagulation in these patients.

In several retrospective analyses, the risk of thromboembolic events was not lower in patients with HF taking warfarin than in patients not treated with antithrombotic drugs.[524,526,527] The use of warfarin was associated with a reduction in major cardiovascular events and death in patients with HF in some studies but not in others.[518,529,530] An RCT that compared the outcome of patients with HF*r*EF assigned to aspirin, warfarin, or clopidogrel was completed,[519] but no therapy appeared to be superior. Another trial compared aspirin with warfarin in patients with reduced LVEF, sinus rhythm, and no cardioembolic source and demonstrated no difference in either the primary outcome of death, stroke, or intracerebral hemorrhage.[520] There was also no difference in the combined outcome of death, ischemic stroke, intracerebral hemorrhage, MI, or HF hospitalization. There was a significant increase in major bleeding with warfarin. Given that there is no overall benefit of warfarin and an increased risk of bleeding, there is no compelling evidence to use warfarin or aspirin in patients with HF*r*EF in the absence of a specific indication.

The efficacy of long-term warfarin for the prevention of stroke in patients with AF is well established. However, the ACCF/AHA guidelines for AF[6] recommend use of the $CHADS_2$ [Congestive heart failure, Hypertension, Age ≥75 years, Diabetes mellitus, previous Stroke/transient ischemic attack (doubled risk weight)] score to assess patient risk for adverse outcomes before initiating anticoagulation therapy. More recently, a revised score, CHADS2-VASc, has been suggested as more applicable to a wider range of patients,[531] but this revised score has not yet been fully studied in patients with HF. Regardless of whether patients receive rhythm or rate control, anticoagulation is recommended for patients with HF and AF for stroke prevention in the presence of at least 1 additional risk factor. For patients with HF and AF in the absence of another cardioembolic risk factor, anticoagulation is reasonable.

Trials of newer oral anticoagulants have compared efficacy and safety with warfarin therapy rather than placebo. Several new oral anticoagulants are now available, including the factor Xa inhibitors apixaban and rivaroxaban and the direct thrombin inhibitor dabigatran.[508,512–514] These drugs have few food and drug interactions compared with warfarin and no need for routine coagulation monitoring or dose adjustment. The fixed dosing together with fewer interactions may simplify patient management, particularly with the polypharmacy commonly seen in HF. These drugs have a potential for an improved benefit–risk profile compared with warfarin, which may increase their use in practice, especially in those at increased bleeding risk. However, important adverse effects have been noted with these new anticoagulants, including gastrointestinal distress, which may limit compliance. At present, there is no commercially available agent to reverse the effect of these newer drugs. Trials comparing new anticoagulants with warfarin have enrolled >10 000 patients with HF. As more detailed evaluations of the comparative benefits and risks of these newer agents in patients with HF are still pending, the writing committee considered their use in patients with HF and nonvalvular AF as an alternative to warfarin to be reasonable.

The benefit afforded by low-dose aspirin in patients with systolic HF but no previous MI or known CAD (or specifically in patients proven free of CAD) remains unknown. A Cochrane review failed to find sufficient evidence to support its use.[532] Retrospective and observational studies again had conflicting results and used very different criteria to identify patients as nonischemic, with some demonstrating protection from aspirin overall[532] or only in patients with more severe depression of systolic function,[518] whereas others found no benefit from aspirin.[530] The high incidence of diabetes mellitus and hypertension in most HF studies, combined with a failure to use objective methods to exclude CAD in enrolled patients, may leave this question unanswered. Currently, data are insufficient to recommend aspirin for empiric primary prevention in HF patients known to be free of atherosclerotic disease and without additional risk factors.

See Online Data Supplement 21 for additional data on anticoagulants.

7.3.2.8.2. Statins: Recommendation
Class III: No Benefit

1. **Statins are not beneficial as adjunctive therapy when prescribed solely for the diagnosis of HF in the absence of other indications for their use.[533–538] *(Level of Evidence: A)***

Statin therapy has been broadly implicated in prevention of adverse cardiovascular events, including new-onset HF. Originally designed to lower cholesterol in patients with cardiovascular disease, statins are increasingly recognized for their favorable effects on inflammation, oxidative stress, and vascular performance. Several observational and post hoc analyses from large clinical trials have implied that statin therapy may provide clinical benefit to patients with HF.[533–536] However, 2 large RCTs have demonstrated that rosuvastatin has neutral effects on long-term outcomes in patients with chronic HF*r*EF when added to standard GDMT.[537,538] At present, statin therapy should not be prescribed primarily for the treatment of HF to improve clinical outcomes.

See Online Data Supplement 22 for additional data on statin therapy.

7.3.2.8.3. Omega-3 Fatty Acids: Recommendation
Class IIa

1. **Omega-3 polyunsaturated fatty acid (PUFA) supplementation is reasonable to use as adjunctive therapy in patients with NYHA class II–IV symptoms and HF*r*EF or HF*p*EF, unless contraindicated, to reduce mortality and cardiovascular hospitalizations.[539,540] *(Level of Evidence: B)***

Supplementation with omega-3 PUFA has been evaluated as an adjunctive therapy for cardiovascular disease and HF.[541] Trials in primary and secondary prevention of coronary heart disease

showed that omega-3 PUFA supplementation results in a 10% to 20% risk reduction in fatal and nonfatal cardiovascular events. The GISSI (Gruppo Italiano per lo Studio della Sopravvivenza nell'Infarto miocardico) Prevenzione trial demonstrated a 21% reduction in death among post-MI patients taking 1 g of omega-3 PUFA (850 mg to 882 mg of eicosapentaenoic acid [EPA] and docosahexaenoic acid [DHA] as ethyl esters in the ratio of 1:1.2).[542] Post hoc subgroup analysis revealed that this reduction in mortality and SCD was concentrated in the approximately 2000 patients with reduced LVEF.[539] The GISSI-HF investigators randomized 6975 patients in NYHA class II–IV chronic HF to 1 g daily of omega-3 PUFA (850 mg to 882 mg EPA/DHA) or matching placebo. Death from any cause was reduced from 29% with placebo to 27% in those treated with omega-3 PUFA.[540] The outcome of death or admission to hospital for a cardiovascular event was also significantly reduced. In reported studies, this therapy has been safe and very well tolerated.[540–543] Further investigations are needed to better define optimal dosing and formulation of omega-3 PUFA supplements. The use of omega-3 PUFA supplementation is reasonable as adjunctive therapy in patients with chronic HF.

See Online Data Supplement 23 for additional data on omega-3 fatty acids.

7.3.2.9. Drugs of Unproven Value or That May Worsen HF: Recommendations

Class III: No Benefit

1. **Nutritional supplements as treatment for HF are not recommended in patients with current or prior symptoms of HF*r*EF.[544,545] *(Level of Evidence: B)***
2. **Hormonal therapies other than to correct deficiencies are not recommended for patients with current or prior symptoms of HF*r*EF. *(Level of Evidence: C)***

Class III: Harm

1. **Drugs known to adversely affect the clinical status of patients with current or prior symptoms of HF*r*EF are potentially harmful and should be avoided or withdrawn whenever possible (eg, most antiarrhythmic drugs, most calcium channel–blocking drugs [except amlodipine], NSAIDs, or thiazolidinediones).[546–557] *(Level of Evidence: B)***
2. **Long-term use of infused positive inotropic drugs is potentially harmful for patients with HF*r*EF, except as palliation for patients with end-stage disease who cannot be stabilized with standard medical treatment (see recommendations for stage D). *(Level of Evidence: C)***

7.3.2.9.1. Nutritional Supplements and Hormonal Therapies. Patients with HF, particularly those treated with diuretics, may become deficient in vitamins and micronutrients. Several nutritional supplements (eg, coenzyme Q10, carnitine, taurine, and antioxidants) and hormonal therapies (eg, growth hormone or thyroid hormone) have been proposed for the treatment of HF.[558–563] Testosterone has also been evaluated for its beneficial effect in HF with modest albeit preliminary effects.[564] Aside from replenishment of documented deficiencies, published data have failed to demonstrate benefit for routine vitamin, nutritional, or hormonal supplementation.[565] In most data or other literature regarding nutraceuticals, there are issues, including outcomes analyses, adverse effects, and drug-nutraceutical interactions, that remain unresolved.

No clinical trials have demonstrated improved survival rates with use of nutritional or hormonal therapy, with the exception of omega-3 fatty acid supplementation as previously noted. Some studies have suggested a possible effect for coenzyme Q10 in reduced hospitalization rates, dyspnea, and edema in patients with HF, but these benefits have not been seen uniformly.[566–569] Because of possible adverse effects and drug interactions of nutritional supplements and their widespread use, clinicians caring for patients with HF should routinely inquire about their use. Until more data are available, nutritional supplements or hormonal therapies are not recommended for the treatment of HF.

7.3.2.9.2. Antiarrhythmic Agents. With atrial and ventricular arrhythmias contributing to the morbidity and mortality of HF, various classes of antiarrhythmic agents have been repeatedly studied in large RCTs. Instead of conferring survival benefit, however, nearly all antiarrhythmic agents increase mortality in the HF population.[548–550] Most antiarrhythmics have some negative inotropic effect and some, particularly the class I and class III antiarrhythmic drugs, have proarrhythmic effects. Hence, class I sodium channel antagonists and the class III potassium channel blockers d-sotalol and dronedarone should be avoided in patients with HF. Amiodarone and dofetilide are the only antiarrhythmic agents to have neutral effects on mortality in clinical trials of patients with HF and thus are the preferred drugs for treating arrhythmias in this patient group.[570–573]

See Online Data Supplement 24 for additional data on antiarrhythmic agents.

7.3.2.9.3. Calcium Channel Blockers: Recommendation

Class III: No Benefit

1. **Calcium channel–blocking drugs are not recommended as routine treatment for patients with HF*r*EF.[551,574,575] *(Level of Evidence: A)***

By reducing peripheral vasoconstriction and LV afterload, calcium channel blockers were thought to have a potential role in the management of chronic HF. However, first-generation dihydropyridine and nondihydropyridine calcium channel blockers also have myocardial depressant activity. Several clinical trials have demonstrated either no clinical benefit or even worse outcomes in patients with HF treated with these drugs.[546,547,551–553] Despite their greater selectivity for calcium channels in vascular smooth muscle cells, second-generation calcium channel blockers, dihydropyridine derivatives such as amlodipine and felodipine, have failed to demonstrate any functional or survival benefit in patients with HF.[575–579] Amlodipine, however, may be considered in the management of hypertension or ischemic heart disease in patients with HF because it is generally well tolerated and had neutral effects on morbidity and mortality in large RCTs. In general, calcium channel blockers should be avoided in patients with HF*r*EF.

See Online Data Supplement 25 for additional data on calcium channel blockers.

7.3.2.9.4. Nonsteroidal Anti-Inflammatory Drugs. NSAIDs inhibit the synthesis of renal prostaglandins, which mediate vasodilation in the kidneys and directly inhibit sodium resorption in the thick ascending loop of Henle and collecting tubule. Hence, NSAIDs can cause sodium and water retention and blunt the effects of diuretics. Several observational cohort studies have revealed increased morbidity and mortality in patients with HF using either nonselective or selective NSAIDs.[554–556,580–582]

See Online Data Supplement 26 for additional data on NSAIDs.

7.3.2.9.5. Thiazolidinediones. Thiazolidinediones increase insulin sensitivity by activating nuclear peroxisome proliferator-activated receptor gamma. Expressed in virtually all tissues, peroxisome proliferator-activated receptor gamma also regulates sodium reabsorption in the collecting ducts of the kidney. In clinical trials, thiazolidinediones have been associated with increased incidence of HF events, even in those without any prior history of clinical HF.[557,583–588]

See Table 19 for a summary of recommendations from this section and Table 20 for strategies for achieving optimal GDMT; see Online Data Supplement 27 for additional data on thiazolidinediones.

7.3.3. Pharmacological Treatment for Stage C HFpEF: Recommendations

See Table 21 for a summary of recommendations from this section.

Class I

1. **Systolic and diastolic blood pressure should be controlled in patients with HF*p*EF in accordance with published clinical practice guidelines to prevent morbidity.[27,91] *(Level of Evidence: B)***
2. **Diuretics should be used for relief of symptoms due to volume overload in patients with HF*p*EF. *(Level of Evidence: C)***

Class IIa

1. **Coronary revascularization is reasonable in patients with CAD in whom symptoms (angina) or demonstrable myocardial ischemia is judged to be having an adverse effect on symptomatic HF*p*EF despite GDMT. *(Level of Evidence: C)***
2. **Management of AF according to published clinical practice guidelines in patients with HF*p*EF is reasonable to improve symptomatic HF (Section 9.1). *(Level of Evidence: C)***
3. **The use of beta-blocking agents, ACE inhibitors, and ARBs in patients with hypertension is reasonable to control blood pressure in patients with HF*p*EF. *(Level of Evidence: C)***

Class IIb

1. **The use of ARBs might be considered to decrease hospitalizations for patients with HF*p*EF.[589] *(Level of Evidence: B)***

Class III: No Benefit

1. **Routine use of nutritional supplements is not recommended for patients with HF*p*EF. *(Level of Evidence: C)***

Trials using comparable and efficacious agents for HF*r*EF have generally been disappointing when used in patients with HF*p*EF.[590] Thus, most of the recommended therapies for HF*p*EF are directed at symptoms, especially comorbidities, and risk factors that may worsen cardiovascular disease.

Blood pressure control concordant with existing hypertension guidelines remains the most important recommendation in patients with HF*p*EF. Evidence from an RCT has shown that improved blood pressure control reduces hospitalization for HF,[591] decreases cardiovascular events, and reduces HF mortality in patients without prevalent HF.[311] In hypertensive patients with HF*p*EF, aggressive treatment (often with several drugs with complementary mechanisms of action) is recommended. ACE inhibitors and/or ARBs are often considered as first-line agents. Specific blood pressure targets in HF*p*EF have not been firmly established; thus, the recommended targets are those used for general hypertensive populations.

CAD is common in patients with HF*p*EF[592]; however, there are no studies to determine the impact of revascularization on symptoms or outcomes specifically in patients with HF*p*EF. In general, contemporary revascularization guidelines[10,12] should be used in the care of patients with HF*p*EF and concomitant CAD. Specific to this population, it might be reasonable to consider revascularization in patients for whom ischemia appears to contribute to HF symptoms, although this determination can be difficult.

Theoretical mechanisms for the worsening of HF symptoms by AF among patients with HF*p*EF include shortened diastolic filling time with tachycardia and the loss of atrial contribution to LV diastolic filling. Conversely, chronotropic incompetence is also a concern. Slowing the heart rate is useful in tachycardia but not in normal resting heart rate; a slow heart rate prolongs diastasis and worsens chronotropic incompetence. Currently, there are no specific trials of rate versus rhythm control in HF*p*EF.

7.3.4. Device Therapy for Stage C HFrEF: Recommendations

See Table 22 for a summary of recommendations from this section.

Class I

1. **ICD therapy is recommended for primary prevention of SCD to reduce total mortality in selected patients with nonischemic DCM or ischemic heart disease at least 40 days post-MI with LVEF of 35% or less and NYHA class II or III symptoms on chronic GDMT, who have reasonable expectation of meaningful survival for more than 1 year.†[355,593] *(Level of Evidence: A)***
2. **CRT is indicated for patients who have LVEF of 35% or less, sinus rhythm, left bundle-branch block (LBBB) with a QRS duration of 150 ms or greater, and NYHA class II, III, or ambulatory IV symptoms on GDMT. *(Level of Evidence: A for NYHA class III/IV[38,78,116,594]; Level of Evidence: B for NYHA class II[595,596])***

†Counseling should be specific to each individual patient and should include documentation of a discussion about the potential for sudden death and nonsudden death from HF or noncardiac conditions. Information should be provided about the efficacy, safety, and potential complications of an ICD and the potential for defibrillation to be inactivated if desired in the future, notably when a patient is approaching end of life. This will facilitate shared decision making between patients, families, and the medical care team about ICDs.[30]

Table 19. Recommendations for Pharmacological Therapy for Management of Stage C HF*r*EF

Recommendations	COR	LOE	References
Diuretics			
Diuretics are recommended in patients with HF*r*EF with fluid retention	I	C	N/A
ACE inhibitors			
ACE inhibitors are recommended for all patients with HF*r*EF	I	A	343, 412–414
ARBs			
ARBs are recommended in patients with HF*r*EF who are ACE inhibitor intolerant	I	A	108, 345, 415, 450
ARBs are reasonable as alternatives to ACE inhibitors as first-line therapy in HF*r*EF	IIa	A	451–456
Addition of an ARB may be considered in persistently symptomatic patients with HF*r*EF on GDMT	IIb	A	420, 457
Routine *combined* use of an ACE inhibitor, ARB, and aldosterone antagonist is potentially harmful	III: Harm	C	N/A
Beta blockers			
Use of 1 of the 3 beta blockers proven to reduce mortality is recommended for all stable patients	I	A	346, 416–419, 448
Aldosterone receptor antagonists			
Aldosterone receptor antagonists are recommended in patients with NYHA class II–IV who have LVEF ≤35%	I	A	425, 426, 478
Aldosterone receptor antagonists are recommended in patients following an acute MI who have LVEF ≤40% with symptoms of HF or DM	I	B	446
Inappropriate use of aldosterone receptor antagonists may be harmful	III: Harm	B	479, 480
Hydralazine and isosorbide dinitrate			
The combination of hydralazine and isosorbide dinitrate is recommended for African Americans with NYHA class III–IV HF*r*EF on GDMT	I	A	423, 424
A combination of hydralazine and isosorbide dinitrate can be useful in patients with HF*r*EF who cannot be given ACE inhibitors or ARBs	IIa	B	449
Digoxin			
Digoxin can be beneficial in patients with HF*r*EF	IIa	B	484–491
Anticoagulation			
Patients with chronic HF with permanent/persistent/paroxysmal AF and an additional risk factor for cardioembolic stroke should receive chronic anticoagulant therapy*	I	A	508–514
The selection of an anticoagulant agent should be individualized	I	C	N/A
Chronic anticoagulation is reasonable for patients with chronic HF who have permanent/persistent/paroxysmal AF but are without an additional risk factor for cardioembolic stroke*	IIa	B	509–511, 515–517
Anticoagulation is not recommended in patients with chronic HF*r*EF without AF, a prior thromboembolic event, or a cardioembolic source	III: No Benefit	B	518–520
Statins			
Statins are not beneficial as adjunctive therapy when prescribed solely for HF	III: No Benefit	A	533–538
Omega-3 fatty acids			
Omega-3 PUFA supplementation is reasonable to use as adjunctive therapy in HF*r*EF or HF*p*EF patients	IIa	B	539, 540
Other drugs			
Nutritional supplements as treatment for HF are not recommended in HF*r*EF	III: No Benefit	B	544, 545
Hormonal therapies other than to correct deficiencies are not recommended in HF*r*EF	III: No Benefit	C	N/A
Drugs known to adversely affect the clinical status of patients with HF*r*EF are potentially harmful and should be avoided or withdrawn	III: Harm	B	546–557
Long-term use of an infusion of a positive inotropic drug is not recommended and may be harmful except as palliation	III: Harm	C	N/A
Calcium channel blockers			
Calcium channel–blocking drugs are not recommended as routine treatment in HF*r*EF	III: No Benefit	A	551, 574, 575

*In the absence of contraindications to anticoagulation.

ACE indicates angiotensin-converting enzyme; AF, atrial fibrillation; ARB, angiotensin-receptor blocker; COR, Class of Recommendation; DM, diabetes mellitus; GDMT, guideline-directed medical therapy; HF, heart failure; HF*p*EF, heart failure with preserved ejection fraction; HF*r*EF, heart failure with reduced ejection fraction; LOE, Level of Evidence; LVEF, left ventricular ejection fraction; MI, myocardial infarction; N/A, not available; NYHA, New York Heart Association; and PUFA, polyunsaturated fatty acids.

Table 20. Strategies for Achieving Optimal GDMT

1. *Uptitrate in small increments* to the recommended target dose or the highest tolerated dose for those medications listed in Table 15 with an appreciation that some patients cannot tolerate the full recommended doses of all medications, particularly patients with low baseline heart rate or blood pressure or with a tendency to postural symptoms.
2. Certain patients (eg, the elderly, patients with chronic kidney disease) may require *more frequent visits and laboratory monitoring during dose titration* and more gradual dose changes. However, such vulnerable patients may accrue considerable benefits from GDMT. Inability to tolerate optimal doses of GDMT may change after disease-modifying interventions such as CRT.
3. *Monitor vital signs closely* before and during uptitration, including postural changes in blood pressure or heart rate, particularly in patients with orthostatic symptoms, bradycardia, and/or "low" systolic blood pressure (eg, 80 to 100 mm Hg).
4. *Alternate adjustments of different medication classes* (especially ACE inhibitors/ARBs and beta blockers) listed in Table 15. Patients with elevated or normal blood pressure and heart rate may tolerate faster incremental increases in dosages.
5. *Monitor renal function and electrolytes* for rising creatinine and hyperkalemia, recognizing that an initial rise in creatinine may be expected and does not necessarily require discontinuation of therapy; discuss tolerable levels of creatinine above baseline with a nephrologist if necessary.
6. Patients may complain of *symptoms of fatigue and weakness* with dosage increases; in the absence of instability in vital signs, reassure them that these symptoms are often transient and usually resolve within a few days of these changes in therapy.
7. *Discourage sudden spontaneous discontinuation of GDMT* medications by the patient and/or other clinicians without discussion with managing clinicians.
8. *Carefully review doses of other medications* for HF symptom control (eg, diuretics, nitrates) during uptitration.
9. *Consider temporary adjustments in dosages of GDMT* during acute episodes of noncardiac illnesses (eg, respiratory infections, risk of dehydration, etc).
10. *Educate patients, family members, and other clinicians* about the expected benefits of achieving GDMT, including an understanding of the potential benefits of myocardial reverse remodeling, increased survival, and improved functional status and HRQOL.

ACE indicates angiotensin-converting enzyme; ARB, angiotensin-receptor blocker; CRT, cardiac resynchronization therapy; GDMT, guideline-directed medical therapy; HF, heart failure; and HRQOL, health-related quality of life.

3. ICD therapy is recommended for primary prevention of SCD to reduce total mortality in selected patients at least 40 days post-MI with LVEF of 30% or less, and NYHA class I symptoms while receiving GDMT, who have reasonable expectation of meaningful survival for more than 1 year.†[362,597,598] *(Level of Evidence: B)*

Class IIa

1. CRT can be useful for patients who have LVEF of 35% or less, sinus rhythm, a non-LBBB pattern with a QRS duration of 150 ms or greater, and NYHA class III/ambulatory class IV symptoms on GDMT.[78,116,594,596] *(Level of Evidence: A)*

2. CRT can be useful for patients who have LVEF of 35% or less, sinus rhythm, LBBB with a QRS duration of 120 to 149 ms, and NYHA class II, III, or ambulatory IV symptoms on GDMT.[78,116,594–596,599] *(Level of Evidence: B)*

3. CRT can be useful in patients with AF and LVEF of 35% or less on GDMT if a) the patient requires ventricular pacing or otherwise meets CRT criteria and b) atrioventricular nodal ablation or pharmacological rate control will allow near 100% ventricular pacing with CRT.[600–605] *(Level of Evidence: B)*

4. CRT can be useful for patients on GDMT who have LVEF of 35% or less and are undergoing placement of a new or replacement device implantation with anticipated requirement for significant (>40%) ventricular pacing.[155,602,606,607] *(Level of Evidence: C)*

†Counseling should be specific to each individual patient and should include documentation of a discussion about the potential for sudden death and nonsudden death from HF or noncardiac conditions. Information should be provided about the efficacy, safety, and potential complications of an ICD and the potential for defibrillation to be inactivated if desired in the future, notably when a patient is approaching end of life. This will facilitate shared decision making between patients, families, and the medical care team about ICDs.[30]

Table 21. Recommendations for Treatment of HF*p*EF

Recommendations	COR	LOE
Systolic and diastolic blood pressure should be controlled according to published clinical practice guidelines	I	B[27,91]
Diuretics should be used for relief of symptoms due to volume overload.	I	C
Coronary revascularization for patients with CAD in whom angina or demonstrable myocardial ischemia is present despite GDMT	IIa	C
Management of AF according to published clinical practice guidelines for HF*p*EF to improve symptomatic HF	IIa	C
Use of beta-blocking agents, ACE inhibitors, and ARBs for hypertension in HF*p*EF	IIa	C
ARBs might be considered to decrease hospitalizations in HF*p*EF	IIb	B[589]
Nutritional supplementation is not recommended in HF*p*EF	III: No Benefit	C

ACE indicates angiotensin-converting enzyme; AF, atrial fibrillation; ARBs, angiotensin-receptor blockers; CAD, coronary artery disease; COR, Class of Recommendation; GDMT, guideline-directed medical therapy; HF, heart failure; HF*p*EF, heart failure with preserved ejection fraction; and LOE, Level of Evidence.

Table 22. Recommendations for Device Therapy for Management of Stage C HF

Recommendations	COR	LOE	References
ICD therapy is recommended for primary prevention of SCD in selected patients with HF*r*EF at least 40 d post-MI with LVEF ≤35% and NYHA class II or III symptoms on chronic GDMT, who are expected to live >1 y*	I	A	355, 593
CRT is indicated for patients who have LVEF ≤35%, sinus rhythm, LBBB with a QRS ≥150 ms, and NYHA class II, III, or ambulatory IV symptoms on GDMT	I	A (NYHA class III/IV)	38, 78, 116, 594
		B (NYHA class II)	595, 596
ICD therapy is recommended for primary prevention of SCD in selected patients with HF*r*EF at least 40 d post-MI with LVEF ≤30% and NYHA class I symptoms while receiving GDMT, who are expected to live >1 y*	I	B	362, 597, 598
CRT can be useful for patients who have LVEF ≤35%, sinus rhythm, a non-LBBB pattern with QRS ≥150 ms, and NYHA class III/ambulatory class IV symptoms on GDMT	IIa	A	78, 116, 594, 596
CRT can be useful for patients who have LVEF ≤35%, sinus rhythm, LBBB with a QRS 120 to 149 ms, and NYHA class II, III, or ambulatory IV symptoms on GDMT	IIa	B	78, 116, 594–596, 599
CRT can be useful in patients with AF and LVEF ≤35% on GDMT if a) the patient requires ventricular pacing or otherwise meets CRT criteria and b) AV nodal ablation or rate control allows near 100% ventricular pacing with CRT	IIa	B	600–605
CRT can be useful for patients on GDMT who have LVEF ≤35% and are undergoing new or replacement device implantation with anticipated ventricular pacing (>40%)	IIa	C	155, 602, 606, 607
An ICD is of uncertain benefit to prolong meaningful survival in patients with a high risk of nonsudden death such as frequent hospitalizations, frailty, or severe comorbidities*	IIb	B	608–611
CRT may be considered for patients who have LVEF ≤35%, sinus rhythm, a non-LBBB pattern with a QRS duration of 120 to 149 ms, and NYHA class III/ambulatory class IV on GDMT	IIb	B	596, 612
CRT may be considered for patients who have LVEF ≤35%, sinus rhythm, a non-LBBB pattern with QRS ≥150 ms, and NYHA class II symptoms on GDMT	IIb	B	595, 596
CRT may be considered for patients who have LVEF ≤30%, ischemic etiology of HF, sinus rhythm, LBBB with QRS ≥150 ms, and NYHA class I symptoms on GDMT	IIb	C	595, 596
CRT is not recommended for patients with NYHA class I or II symptoms and non-LBBB pattern with QRS <150 ms	III: No Benefit	B	595, 596, 612
CRT is not indicated for patients whose comorbidities and/or frailty limit survival to <1 y	III: No Benefit	C	38

*Counseling should be specific to each individual patient and should include documentation of a discussion about the potential for sudden death and nonsudden death from HF or noncardiac conditions. Information should be provided about the efficacy, safety, and potential complications of an ICD and the potential for defibrillation to be inactivated if desired in the future, notably when a patient is approaching end of life. This will facilitate shared decision making between patients, families, and the medical care team about ICDs.[30]

AF indicates atrial fibrillation; AV, atrioventricular; COR, Class of Recommendation; CRT, cardiac resynchronization therapy; GDMT, guideline-directed medical therapy; HF, heart failure; HF*r*EF, heart failure with reduced ejection fraction; ICD, implantable cardioverter-defibrillator; LBBB, left bundle-branch block; LOE, Level of Evidence; LVEF, left ventricular ejection fraction; MI, myocardial infarction; NYHA, New York Heart Association; and SCD, sudden cardiac death.

Class IIb

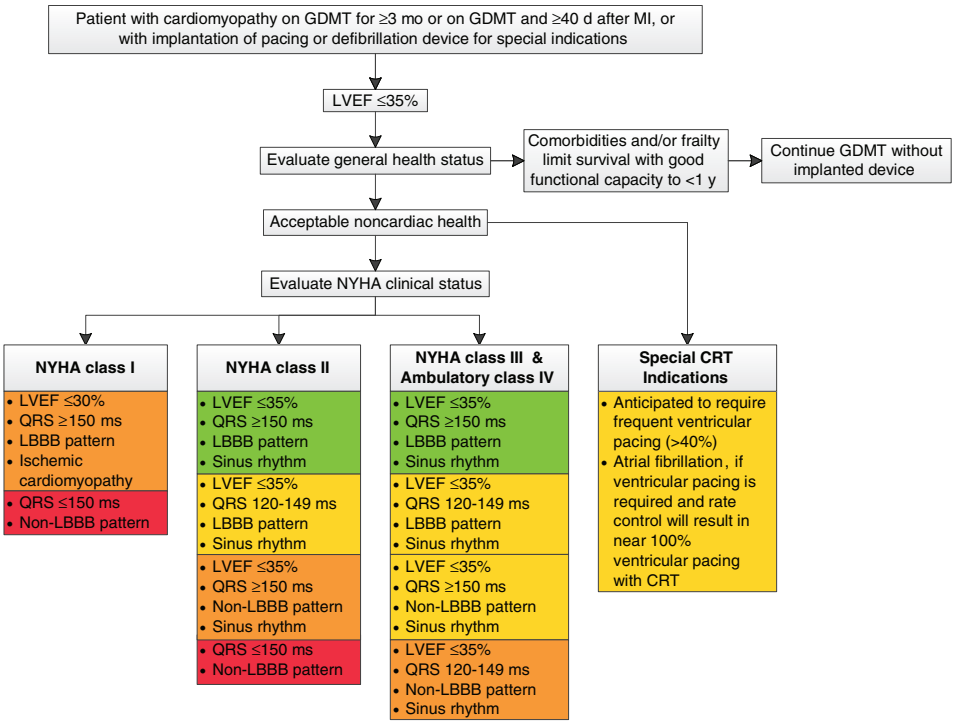
1. **The usefulness of implantation of an ICD is of uncertain benefit to prolong meaningful survival in patients with a high risk of nonsudden death as predicted by frequent hospitalizations, advanced frailty, or comorbidities such as systemic malignancy or severe renal dysfunction.†[608–611] *(Level of Evidence: B)***
2. **CRT may be considered for patients who have LVEF of 35% or less, sinus rhythm, a non-LBBB pattern with QRS duration of 120 to 149 ms, and NYHA class III/ambulatory class IV on GDMT.[596,612] *(Level of Evidence: B)***
3. **CRT may be considered for patients who have LVEF of 35% or less, sinus rhythm, a non-LBBB pattern with a QRS duration of 150 ms or greater, and NYHA class II symptoms on GDMT.[595,596] *(Level of Evidence: B)***
4. **CRT may be considered for patients who have LVEF of 30% or less, ischemic etiology of HF, sinus rhythm, LBBB with a QRS duration of 150 ms or greater, and NYHA class I symptoms on GDMT.[595,596] *(Level of Evidence: C)***

Class III: No Benefit

1. **CRT is not recommended for patients with NYHA class I or II symptoms and non-LBBB pattern with QRS duration less than 150 ms.[595,596,612] *(Level of Evidence: B)***
2. **CRT is not indicated for patients whose comorbidities and/or frailty limit survival with good functional capacity to less than 1 year.[38] *(Level of Evidence: C)***

See Figure 2, indications for CRT therapy algorithm.

†Counseling should be specific to each individual patient and should include documentation of a discussion about the potential for sudden death and nonsudden death from HF or noncardiac conditions. Information should be provided about the efficacy, safety, and potential complications of an ICD and the potential for defibrillation to be inactivated if desired in the future, notably when a patient is approaching end of life. This will facilitate shared decision making between patients, families, and the medical care team about ICDs.[30]



Colors correspond to the class of recommendations in the ACCF/AHA Table 1.

Benefit for NYHA class I and II patients has only been shown in CRT-D trials, and while patients may not experience immediate symptomatic benefit, late remodeling may be avoided along with long-term HF consequences. There are no trials that support CRT-pacing (without ICD) in NYHA class I and II patients. Thus, it is anticipated these patients would receive CRT-D unless clinical reasons or personal wishes make CRT-pacing more appropriate. In patients who are NYHA class III and ambulatory class IV, CRT-D may be chosen but clinical reasons and personal wishes may make CRT-pacing appropriate to improve symptoms and quality of life when an ICD is not expected to produce meaningful benefit in survival.

Figure 2. Indications for CRT therapy algorithm. CRT indicates cardiac resynchronization therapy; CRT-D, cardiac resynchronization therapy-defibrillator; GDMT, guideline-directed medical therapy; HF, heart failure; ICD, implantable cardioverter-defibrillator; LBBB, left bundle-branch block; LVEF, left ventricular ejection fraction; MI, myocardial infarction; and NYHA, New York Heart Association.

7.3.4.1. Implantable Cardioverter-Defibrillator

Patients with reduced LVEF are at increased risk for ventricular tachyarrhythmias leading to SCD. Sudden death in HF*r*EF has been substantially decreased by neurohormonal antagonists that alter disease progression and also protect against arrhythmias. Nonetheless, patients with systolic dysfunction remain at increased risk for SCD due to ventricular tachyarrhythmias. Patients who have had sustained ventricular tachycardia, ventricular fibrillation, unexplained syncope, or cardiac arrest are at highest risk for recurrence. Indications for ICD therapy as secondary prevention of SCD in these patients are also discussed in the ACCF/AHA/HRS device-based therapy guideline.[4]

The use of ICDs for primary prevention of SCD in patients with HF*r*EF without prior history of arrhythmias or syncope has been evaluated in multiple RCTs. ICD therapy for primary prevention was demonstrated to reduce all-cause mortality. For patients with LVEF ≤30% after remote MI, use of ICD therapy led to a 31% decrease in mortality over 20 months, for an absolute decrease of 5.6%.[362] For patients with mild to moderate symptoms of HF with LVEF ≤35% due either to ischemic or nonischemic etiology, there was a 23% decrease in mortality over a 5-year period, for an absolute decrease of 7.2%.[593] For both these trials, the survival benefit appeared after the first year. Other smaller trials were consistent with this degree of benefit, except for patients within the first 40 days after acute MI, in whom SCD was decreased but there was an increase in other events such that there was no net benefit for survival.[598,614] Both SCD and total mortality are highest in patients with HF*r*EF with class IV symptoms, in whom ICDs are not expected to prolong meaningful survival and are not indicated except in those for whom heart transplantation or MCS is anticipated.

The use of ICDs for primary prevention in patients with HF*r*EF should be considered only in the setting of optimal GDMT and with a minimum of 3 to 6 months of appropriate medical therapy. A repeat assessment of ventricular function is appropriate to assess any recovery of ventricular function on GDMT that would be above the threshold where an ICD is indicated. This therapy will often improve ventricular function to a range for which the risk of sudden death is too low to warrant placement of an ICD. In addition, the trials of ICDs for primary prevention of SCD studied patients who were already on GDMT.

ICDs are highly effective in preventing death from ventricular arrhythmias, but frequent shocks can decrease HRQOL and lead to posttraumatic stress syndrome.[615] Therapy with antiarrhythmic drugs and catheter ablation for ventricular tachycardia can decrease the number of ICD shocks given and can sometimes improve ventricular function in cases of very frequent ventricular tachyarrhythmias. Refined device programming can optimize pacing therapies to avert the need for shocks, minimize inappropriate shocks, and avoid aggravation of HF by frequent ventricular pacing. Although there have been occasional recalls of device generators, these are exceedingly rare in comparison to complications related to intracardiac device leads, such as fracture and infection.

ICDs are indicated only in patients with a reasonable expectation of survival with good functional status beyond a year, but the range of uncertainty remains wide. The complex decision about the relative risks and benefits of ICDs for primary prevention of SCD must be individualized for each patient. Unlike other therapies that can prolong life with HF, the ICD does not modify the disease except in conjunction with CRT. Patients with multiple comorbidities have a higher rate of implant complications and higher competing risks of death from noncardiac causes.[616] Older patients, who are at a higher risk of nonsudden death, are often underrepresented in the pivotal trials where the average patient is <65 years of age.[617] The major trials for secondary prevention of SCD showed no benefit in patients >75 years of age,[618] and a meta-analysis of primary prevention of SCD also suggested lesser effectiveness of ICDs.[619] Populations of patients with multiple HF hospitalizations, particularly in the setting of chronic kidney disease, have a median survival rate of <2 years, during which the benefit of the ICD may not be realized.[608] There is widespread recognition of the need for further research to identify patients most and least likely to benefit from ICDs for primary prevention of SCD in HF. Similar considerations apply to the decision to replace the device generator.

Consideration of ICD implantation is highly appropriate for shared decision making.[30] The risks and benefits carry different relative values depending on patient goals and preferences. Discussion should include the potential for SCD and nonsudden death from HF or noncardiac conditions. Information should be provided in a format that patients can understand about the estimated efficacy, safety, and potential complications of an ICD and the ease with which defibrillation can be inactivated if no longer desired.[620] As the prevalence of implantable devices increases, it is essential that clearly defined processes be in place to support patients and families when decisions about deactivation arise.[621]

7.3.4.2. Cardiac Resynchronization Therapy

In approximately one third of patients, HF progression is accompanied by substantial prolongation of the QRS interval, which is associated with worse outcome.[622] Multisite ventricular pacing (termed CRT or biventricular pacing) can improve ventricular contractile function, diminish secondary mitral regurgitation, reverse ventricular remodeling, and sustain improvement in LVEF. Increased blood pressure with CRT can allow increased titration of neurohormonal antagonist medications that may further contribute to improvement. Benefits were proven initially in trials of patients with NYHA class III or ambulatory class IV HF symptoms and QRS duration of ≥120 to 130 ms. These results have included a decrease of approximately 30% in rehospitalization and reductions in all-cause mortality in the range of 24% to 36%. Improvement in survival is evident as early as the first 3 months of therapy. Functional improvements have been demonstrated on average as a 1 to 2 mL/kg/min increase in peak oxygen consumption, 50- to 70-meter increase in 6-minute walk distance, and a reduction of 10 points or more in the 0- to 105-point scale of the Minnesota Living With Heart Failure Questionnaire, all considered clinically significant. These results include patients with a wide range of QRS duration and, in most cases, sinus rhythm.[78,116,594,623]

Although it is still not possible to predict with confidence which patients will improve with CRT, further experiences have provided some clarification. Benefit appears confined largely to patients with a QRS duration of at least 150 ms and LBBB pattern.[624–628] The weight of the evidence has been accumulated from patients with sinus rhythm, with meta-analyses indicating substantially less clinical benefit in patients with permanent AF.[604,605] Because effective CRT requires a high rate of ventricular pacing,[629] the benefit for patients with AF is most evident in patients who have undergone atrioventricular nodal ablation, which ensures obligate ventricular pacing.[601–603]

In general, most data derive from patients with class III symptoms. Patients labeled as having class IV symptoms account for a small minority of patients enrolled. Furthermore, these patients, characterized as "ambulatory" NYHA class IV, are not refractory due to fluid retention, frequently hospitalized for HF, or dependent on continuous intravenous inotropic therapy. CRT should not be considered as "rescue" therapy for stage D HF. In addition, patients with significant noncardiac limitations are unlikely to derive major benefit from CRT.

Since publication of the 2009 HF guideline,[38] new evidence supports extension of CRT to patients with milder symptoms. LV remodeling was consistently reversed or halted, with benefit also in reduction of HF hospitalizations.[595,596,599] In this population with low 1-year mortality, reduction of HF hospitalization dominated the composite primary endpoints, but a mortality benefit was subsequently observed in a 2-year extended follow-up study[630] and in a meta-analysis of 5 trials of CRT in mild HF that included 4213 patients with class II symptoms.[631] Overall benefits in class II HF were noted only in patients with QRS ≥150 ms and LBBB, with an adverse impact with shorter QRS duration or non-LBBB.

The entry criterion for LVEF in CRT trials has ranged from ≤30% to ≤40%. The trials with class III–IV symptoms included patients with LVEF ≤35%.[78,116,594] The 2 individual trials showing improvement in mortality with class II HF included patients with LVEF ≤30%.[632,633] Trials demonstrating significant improvement in LV size and EF have included patients with LVEF ≤35%[115] and LVEF ≤40%,[599] which also showed reduction in the secondary endpoint of time to hospitalization and a reduction in the composite of clinical HF events comparable to that of all of the CRT trials.[624] The congruence of evidence from the totality of CRT trials with regard to remodeling and HF events supports a common threshold of 35% for benefit from CRT in patients with class II, III, and IV HF symptoms. For patients with class II HF, all but 1 of the trials tested CRT in combination with an ICD, whereas there is evidence for benefit with both CRT-defibrillator and CRT alone in patients with class III–IV symptoms.[78,116]

Although the weight of evidence is substantial for patients with class II symptoms, these CRT trials have included only 372 patients with class I symptoms, most with concomitant ICD for the postinfarction indication.[595,599] Considering the risk–benefit ratio for class I, more concern is raised by the early adverse events, which in 1 trial occurred in 13% of patients with CRT-ICD compared with 6.7% in patients with ICD only.[596] On the basis of limited data from MADIT-CRT (Multicenter Automatic Defibrillator Implantation Trial-Cardiac Resynchronization Therapy), CRT-ICD may be

considered for patients with class I symptoms >40 days after MI, LVEF ≤30%, sinus rhythm, LBBB, and QRS ≥150 ms.[595]

These indications for CRT all include expectation for ongoing GDMT and diuretic therapy as needed for fluid retention. In addition, regular monitoring is required after device implantation because adjustment of HF therapies and reprogramming of device intervals may be required. The trials establishing the benefit of these interventions were conducted in centers offering expertise in both implantation and follow-up. Recommendations for CRT are made with the expectation that they will be performed in centers with expertise and outcome comparable to that of the trials that provide the bases of evidence. The benefit–risk ratio for this intervention would be anticipated to be diminished for patients who do not have access to these specialized care settings or who are nonadherent.

See Online Data Supplements 28 and 29 for additional data on device therapy and CRT.

7.4. Stage D

7.4.1. Definition of Advanced HF

A subset of patients with chronic HF will continue to progress and develop persistently severe symptoms despite maximum GDMT. Various terminologies have been used to describe this group of patients who are classified with ACCF/AHA stage D HF, including "advanced HF," "end-stage HF," and "refractory HF." In the 2009 ACCF/AHA HF guideline, stage D was defined as "patients with truly refractory HF who might be eligible for specialized, advanced treatment strategies, such as MCS, procedures to facilitate fluid removal, continuous inotropic infusions, or cardiac transplantation or other innovative or experimental surgical procedures, or for end-of-life care, such as hospice."[38] The European Society of Cardiology has developed a definition of advanced HF with objective criteria that can be useful[32] (Table 23). There are clinical clues that may assist clinicians in identifying patients who are progressing toward advanced HF (Table 24). The Interagency Registry for Mechanically Assisted Circulatory Support (INTERMACS) has developed 7 profiles that further stratify patients with advanced HF (Table 25).[635]

Table 23. ESC Definition of Advanced HF

1. Severe symptoms of HF with dyspnea and/or fatigue at rest or with minimal exertion (NYHA class III or IV)
2. Episodes of fluid retention (pulmonary and/or systemic congestion, peripheral edema) and/or reduced cardiac output at rest (peripheral hypoperfusion)
3. Objective evidence of severe cardiac dysfunction shown by at least 1 of the following:
   a. LVEF <30%
   b. Pseudonormal or restrictive mitral inflow pattern
   c. Mean PCWP >16 mm Hg and/or RAP >12 mm Hg by PA catheterization
   d. High BNP or NT-proBNP plasma levels in the absence of noncardiac causes
4. Severe impairment of functional capacity shown by 1 of the following:
   a. Inability to exercise
   b. 6-Minute walk distance ≤300 m
   c. Peak $\dot{V}O_2$ <12 to 14 mL/kg/min
5. History of ≥1 HF hospitalization in past 6 mo
6. Presence of all the previous features despite "attempts to optimize" therapy, including diuretics and GDMT, unless these are poorly tolerated or contraindicated, and CRT when indicated

BNP indicates B-type natriuretic peptide; CRT, cardiac resynchronization therapy; ESC, European Society of Cardiology; GDMT, guideline-directed medical therapy; HF, heart failure; LVEF, left ventricular ejection fraction; NT-proBNP, N-terminal pro-B-type natriuretic peptide; NYHA, New York Heart Association; PA, pulmonary artery; PWCP, pulmonary capillary wedge pressure; and RAP, right atrial pressure.

Adapted from Metra et al.[32]

Table 24. Clinical Events and Findings Useful for Identifying Patients With Advanced HF

Repeated (≥2) hospitalizations or ED visits for HF in the past year
Progressive deterioration in renal function (eg, rise in BUN and creatinine)
Weight loss without other cause (eg, cardiac cachexia)
Intolerance to ACE inhibitors due to hypotension and/or worsening renal function
Intolerance to beta blockers due to worsening HF or hypotension
Frequent systolic blood pressure <90 mm Hg
Persistent dyspnea with dressing or bathing requiring rest
Inability to walk 1 block on the level ground due to dyspnea or fatigue
Recent need to escalate diuretics to maintain volume status, often reaching daily furosemide equivalent dose >160 mg/d and/or use of supplemental metolazone therapy
Progressive decline in serum sodium, usually to <133 mEq/L
Frequent ICD shocks

ACE indicates angiotensin-converting enzyme; BUN, blood urea nitrogen; ED, emergency department; HF, heart failure; and ICD, implantable cardioverter-defibrillator.

Adapted from Russell et al.[642]

7.4.2. Important Considerations in Determining If the Patient Is Refractory

Patients considered to have stage D HF should be thoroughly evaluated to ascertain that the diagnosis is correct and that there are no remediable etiologies or alternative explanations for advanced symptoms. For example, it is important to determine that HF and not a concomitant pulmonary disorder is the basis of dyspnea. Similarly, in those with presumed cardiac cachexia, other causes of weight loss should be ruled out. Likewise, other reversible factors such as thyroid disorders should be treated. Severely symptomatic patients presenting with a new diagnosis of HF can often improve substantially if they are initially stabilized. Patients should also be evaluated for nonadherence to medications,[636–639] sodium restriction,[640] and/or daily weight monitoring.[641] Finally, a careful review of prior medical management should be conducted to verify that all evidence-based therapies likely to improve clinical status have been considered.

See Online Data Supplements 30 and 31 for additional data on therapies—important considerations and sildenafil.

7.4.3. Water Restriction: Recommendation

Class IIa

1. **Fluid restriction (1.5 to 2 L/d) is reasonable in stage D, especially in patients with hyponatremia, to reduce congestive symptoms. *(Level of Evidence: C)***

Recommendations for fluid restriction in HF are largely driven by clinical experience. Sodium and fluid balance recommendations are best implemented in the context of weight and symptom monitoring programs. Routine strict fluid restriction in all

Table 25. INTERMACS Profiles

Profile*	Profile Description	Features
1	Critical cardiogenic shock ("Crash and burn")	Life-threatening hypotension and rapidly escalating inotropic/pressor support, with critical organ hypoperfusion often confirmed by worsening acidosis and lactate levels.
2	Progressive decline ("Sliding fast" on inotropes)	"Dependent" on inotropic support but nonetheless shows signs of continuing deterioration in nutrition, renal function, fluid retention, or other major status indicator. Can also apply to a patient with refractory volume overload, perhaps with evidence of impaired perfusion, in whom inotropic infusions *cannot be maintained* due to tachyarrhythmias, clinical ischemia, or other intolerance.
3	Stable but inotrope dependent	Clinically stable on mild-moderate doses of intravenous inotropes (or has a temporary circulatory support device) after repeated documentation of failure to wean without symptomatic hypotension, worsening symptoms, or progressive organ dysfunction (usually renal).
4	Resting symptoms on oral therapy at home	Patient who is at home on oral therapy but frequently has symptoms of congestion at rest or with activities of daily living (dressing or bathing). He or she may have orthopnea, shortness of breath during dressing or bathing, gastrointestinal symptoms (abdominal discomfort, nausea, poor appetite), disabling ascites, or severe lower-extremity edema.
5	Exertion intolerant ("housebound")	Patient who is comfortable at rest but unable to engage in any activity, living predominantly within the house or housebound.
6	Exertion limited ("walking wounded")	Patient who is comfortable at rest without evidence of fluid overload but who is able to do some mild activity. Activities of daily living are comfortable and minor activities outside the home such as visiting friends or going to a restaurant can be performed, but fatigue results within a few minutes or with any meaningful physical exertion.
7	Advanced NYHA class III	Patient who is clinically stable with a reasonable level of comfortable activity, despite a history of previous decompensation that is not recent. This patient is usually able to walk more than a block. Any decompensation requiring intravenous diuretics or hospitalization within the previous month should make this person a Patient Profile 6 or lower.

*Modifier options: Profiles 3–6 can be modified with the designation frequent flyer for patients with recurrent decompensations leading to frequent (generally at least 2 in last 3 mo or 3 in last 6 mo) emergency department visits or hospitalizations for intravenous diuretics, ultrafiltration, or brief inotropic therapy. Profile 3 can be modified in this fashion if the patient is usually at home. If a Profile 7 patient meets the definition of frequent flyer, the patient should be moved to Profile 6 or worse. Other modifier options include arrhythmia, which should be used in the presence of recurrent ventricular tachyarrhythmias contributing to the overall clinical course (eg, frequent implantable cardioverter-defibrillator shocks or requirement of external defibrillation, usually more than twice weekly); or temporary circulatory support for hospitalized patients profiles 1–3.[635]

INTERMACS indicates Interagency Registry for Mechanically Assisted Circulatory Support; and NYHA, New York Heart Association.

Adapted from Stevenson et al.[643]

patients with HF regardless of symptoms or other considerations does not appear to result in significant benefit.[644] Limiting fluid intake to around 2 L/d is usually adequate for most hospitalized patients who are not diuretic resistant or significantly hyponatremic. In 1 study, patients on a similar sodium and diuretic regimen showed higher readmission rates with higher fluid intake, suggesting that fluid intake affects HF outcomes.[385] Strict fluid restriction may best be used in patients who are either refractory to diuretics or have hyponatremia. Fluid restriction, especially in conjunction with sodium restriction, enhances volume management with diuretics. Fluid restriction is important to manage hyponatremia, which is relatively common with advanced HF and portends a poor prognosis.[645,646] Fluid restriction may improve serum sodium concentration; however, it is difficult to achieve and maintain. In hot or low-humidity climates, excessive fluid restriction predisposes patients with advanced HF to the risk of heat stroke. Hyponatremia in HF is primarily due to an inability to excrete free water. Norepinephrine and angiotensin II activation result in decreased sodium delivery to the distal tubule, whereas arginine vasopressin increases water absorption from the distal tubule. In addition, angiotensin II also promotes thirst. Thus, sodium and fluid restriction in advanced patients with HF is important.

7.4.4. Inotropic Support: Recommendations

Class I

1. **Until definitive therapy (eg, coronary revascularization, MCS, heart transplantation) or resolution of the acute precipitating problem, patients with cardiogenic shock should receive temporary intravenous inotropic support to maintain systemic perfusion and preserve end-organ performance.** ***(Level of Evidence: C)***

Class IIa

1. **Continuous intravenous inotropic support is reasonable as "bridge therapy" in patients with stage D HF refractory to GDMT and device therapy who are eligible for and awaiting MCS or cardiac transplantation.[647,648]** ***(Level of Evidence: B)***

Class IIb

1. **Short-term, continuous intravenous inotropic support may be reasonable in those hospitalized patients presenting with documented severe systolic dysfunction who present with low blood pressure and significantly depressed cardiac output to maintain systemic perfusion and preserve end-organ performance.[592,649,650]** ***(Level of Evidence: B)***
2. **Long-term, continuous intravenous inotropic support may be considered as palliative therapy for symptom control in select patients with stage D HF despite optimal GDMT and device therapy who are not eligible for either MCS or cardiac transplantation.[651–653]** ***(Level of Evidence: B)***

Class III: Harm

1. **Long-term use of either continuous or intermittent, intravenous parenteral positive inotropic agents, in the absence of specific indications or for reasons**

Table 26. Intravenous Inotropic Agents Used in Management of HF

Inotropic Agent	Dose (mcg/kg)		Drug Kinetics and Metabolism	Effects				Adverse Effects	Special Considerations
	Bolus	Infusion (/min)		CO	HR	SVR	PVR		
Adrenergic agonists									
Dopamine	N/A	5 to 10	$t_{1/2}$: 2 to 20 min R,H,P	↑	↑	↔	↔	T, HA, N, tissue necrosis	Caution: MAO-I
	N/A	10 to 15		↑	↑	↑	↔		
Dobutamine	N/A	2.5 to 5	$t_{1/2}$: 2 to 3 min H	↑	↑	↓	↔	↑/↓BP, HA, T, N, F, hypersensitivity	Caution: MAO-I; CI: sulfite allergy
	N/A	5 to 20		↑	↑	↔	↔		
PDE inhibitor									
Milrinone	N/R	0.125 to 0.75	$t_{1/2}$: 2.5 h H	↑	↑	↓	↓	T, ↓BP	Renal dosing, monitor LFTs

BP indicates blood pressure; CI, contraindication; CO, cardiac output; F, fever; H, hepatic; HA, headache; HF, heart failure; HR, heart rate; LFT, liver function test; MAO-I, monoamine oxidase inhibitor; N, nausea; N/A, not applicable; N/R, not recommended; P, plasma; PDE, phosphodiesterase; PVR, pulmonary vascular resistance; R, renal; SVR, systemic vascular resistance; T, tachyarrhythmias; and $t_{1/2}$, elimination half-life.

other than palliative care, is potentially harmful in the patient with HF.[416,654–659] *(Level of Evidence: B)*

2. **Use of parenteral inotropic agents in hospitalized patients without documented severe systolic dysfunction, low blood pressure, or impaired perfusion and evidence of significantly depressed cardiac output, with or without congestion, is potentially harmful.[592,649,650] *(Level of Evidence: B)***

Despite improving hemodynamic compromise, positive inotropic agents have not demonstrated improved outcomes in patients with HF in either the hospital or outpatient setting.[416,654–658] Regardless of their mechanism of action (eg, inhibition of phosphodiesterase, stimulation of adrenergic or dopaminergic receptors, calcium sensitization), chronic oral inotrope treatment increased mortality, mostly related to arrhythmic events. Parenteral inotropes, however, remain as an option to help the subset of patients with HF who are refractory to other therapies and are suffering consequences from end-organ hypoperfusion. Inotropes should be considered only in such patients with systolic dysfunction who have low cardiac index and evidence of systemic hypoperfusion and/or congestion (Table 26). To minimize adverse effects, lower doses are preferred. Similarly, the ongoing need for inotropic support and the possibility of discontinuation should be regularly assessed.

See Online Data Supplements 32 and 33 for additional data on inotropes.

7.4.5. Mechanical Circulatory Support: Recommendations

Class IIa

1. **MCS is beneficial in carefully selected‡ patients with stage D HF*r*EF in whom definitive management (eg, cardiac transplantation) or cardiac recovery is anticipated or planned.[660–667] *(Level of Evidence: B)***
2. **Nondurable MCS, including the use of percutaneous and extracorporeal ventricular assist devices (VADs), is reasonable as a "bridge to recovery" or "bridge to decision" for carefully selected‡ patients with HF*r*EF with acute, profound hemodynamic compromise.[668–671] *(Level of Evidence: B)***
3. **Durable MCS is reasonable to prolong survival for carefully selected‡ patients with stage D HF*r*EF.[672–675] *(Level of Evidence: B)***

MCS has emerged as a viable therapeutic option for patients with advanced stage D HF*r*EF refractory to optimal GDMT and cardiac device intervention. Since its initial use 50 years ago for postcardiotomy shock,[676] the implantable VAD continues to evolve.

Designed to assist the native heart, VADs are differentiated by the implant location (intracorporeal versus extracorporeal), approach (percutaneous versus surgical), flow characteristic (pulsatile versus continuous), pump mechanism (volume displacement, axial, centrifugal), and the ventricle(s) supported (left, right, biventricular). VADs are effective in both the short-term (hours to days) management of acute decompensated, hemodynamically unstable HF*r*EF that is refractory to inotropic support, and the long-term (months to years) management of stage D chronic HF*r*EF. Nondurable or temporary, MCS provides an opportunity for decisions about the appropriateness of transition to definitive management such as cardiac surgery or durable, that is, permanent, MCS or, in the case of improvement and recovery, suitability for device removal. Nondurable MCS thereby may be helpful as either a bridge to decision or a bridge to recovery.

More common scenarios for MCS, however, are long-term strategies, including 1) bridge to transplantation, 2) bridge to candidacy, and 3) destination therapy. Bridge to transplant and destination therapy have the strongest evidence base with respect to survival, functional capacity, and HRQOL benefits.

Data from INTERMACS provides valuable information on risk factors and outcomes for patients undergoing MCS.

‡Although optimal patient selection for MCS remains an active area of investigation, general indications for referral for MCS therapy include patients with LVEF <25% and NYHA class III–IV functional status despite GDMT, including, when indicated, CRT, with either high predicted 1- to 2-year mortality (eg, as suggested by markedly reduced peak oxygen consumption and clinical prognostic scores) or dependence on continuous parenteral inotropic support. Patient selection requires a multidisciplinary team of experienced advanced HF and transplantation cardiologists, cardiothoracic surgeons, nurses, and ideally, social workers and palliative care clinicians.

The greatest risk factors for death among patients undergoing bridge to transplant include acuity and severity of clinical condition and evidence of right ventricular failure.[677] MCS may also be used as a bridge to candidacy. Retrospective studies have shown reduction in pulmonary pressures with MCS therapy in patients with HF considered to have "fixed" pulmonary hypertension.[661–663] Thus, patients who may be transplant-ineligible due to irreversible severe pulmonary hypertension may become eligible with MCS support over time. Other bridge-to-candidacy indications may include obesity and tobacco use in patients who are otherwise candidates for cardiac transplantation. There is ongoing interest in understanding how MCS facilitates LV reverse remodeling. Current scientific and translational research in the area aims to identify clinical, cellular, molecular, and genomic markers of cardiac recovery in the patient with VAD.[678,679]

See Online Data Supplements 34 and 35 for additional data on MCS and left VADs.

7.4.6. Cardiac Transplantation: Recommendation

Class I

1. **Evaluation for cardiac transplantation is indicated for carefully selected patients with stage D HF despite GDMT, device, and surgical management.[680] *(Level of Evidence: C)***

Cardiac transplantation is considered the gold standard for the treatment of refractory end-stage HF. Since the first successful cardiac transplantation in 1967, advances in immunosuppressive therapy have vastly improved the long-term survival of transplant recipients with a 1-, 3-, and 5-year post-transplant survival rate of 87.8%, 78.5%, and 71.7% in adults, respectively.[681] Similarly, cardiac transplantation has been shown to improve functional status and HRQOL.[682–688] The greatest survival benefit is seen in those patients who are at highest risk of death from advanced HF.[689] Cardiopulmonary exercise testing helps refine candidate selection.[690–696] Data suggest acceptable posttransplant outcomes in patients with reversible pulmonary hypertension,[697] hypertrophic cardiomyopathy,[698] peripartum cardiomyopathy,[699] restrictive cardiomyopathy,[700,701] and muscular dystrophy.[702] Selected patients with stage D HF and poor prognosis should be referred to a cardiac transplantation center for evaluation and transplant consideration. Determination of HF prognosis is addressed in Sections 6.1.2 and 7.4.2. The listing criteria and evaluation and management of patients undergoing cardiac transplantation are described in detail by the International Society for Heart and Lung Transplantation.[680]

See Table 27 for a summary of recommendations from this section, Figure 3 for the stages of HF development; and Online Data Supplement 36 for additional data on transplantation.

Table 27. Recommendations for Inotropic Support, MCS, and Cardiac Transplantation

Recommendations	COR	LOE	References
Inotropic support			
Cardiogenic shock pending definitive therapy or resolution	I	C	N/A
BTT or MCS in stage D refractory to GDMT	IIa	B	647, 648
Short-term support for threatened end-organ dysfunction in hospitalized patients with stage D and severe HF*r*EF	IIb	B	592, 649, 650
Long-term support with continuous infusion palliative therapy in select stage D HF	IIb	B	651–653
Routine intravenous use, either continuous or intermittent, is potentially harmful in stage D HF	III: Harm	B	416, 654–659
Short-term intravenous use in hospitalized patients without evidence of shock or threatened end-organ performance is potentially harmful	III: Harm	B	592, 649, 650
MCS			
MCS is beneficial in carefully selected* patients with stage D HF in whom definitive management (eg, cardiac transplantation) is anticipated or planned	IIa	B	660–667
Nondurable MCS is reasonable as a "bridge to recovery" or "bridge to decision" for carefully selected* patients with HF and acute profound disease	IIa	B	668–671
Durable MCS is reasonable to prolong survival for carefully selected* patients with stage D HF*r*EF	IIa	B	672–675
Cardiac transplantation			
Evaluation for cardiac transplantation is indicated for carefully selected patients with stage D HF despite GDMT, device, and surgical management	I	C	680

*Although optimal patient selection for MCS remains an active area of investigation, general indications for referral for MCS therapy include patients with LVEF <25% and NYHA class III–IV functional status despite GDMT, including, when indicated, CRT, with either high predicted 1- to 2-year mortality (eg, as suggested by markedly reduced peak oxygen consumption and clinical prognostic scores) or dependence on continuous parenteral inotropic support. Patient selection requires a multidisciplinary team of experienced advanced HF and transplantation cardiologists, cardiothoracic surgeons, nurses and ideally, social workers and palliative care clinicians.

BTT indicates bridge to transplant; COR, Class of Recommendation; CRT, cardiac resynchronization therapy; GDMT, guideline-directed medical therapy; HF, heart failure; HF*r*EF, heart failure with reduced ejection fraction; LOE, Level of Evidence; LVEF, left ventricular ejection fraction; MCS, mechanical circulatory support; N/A, not applicable; and NYHA, New York Heart Association.

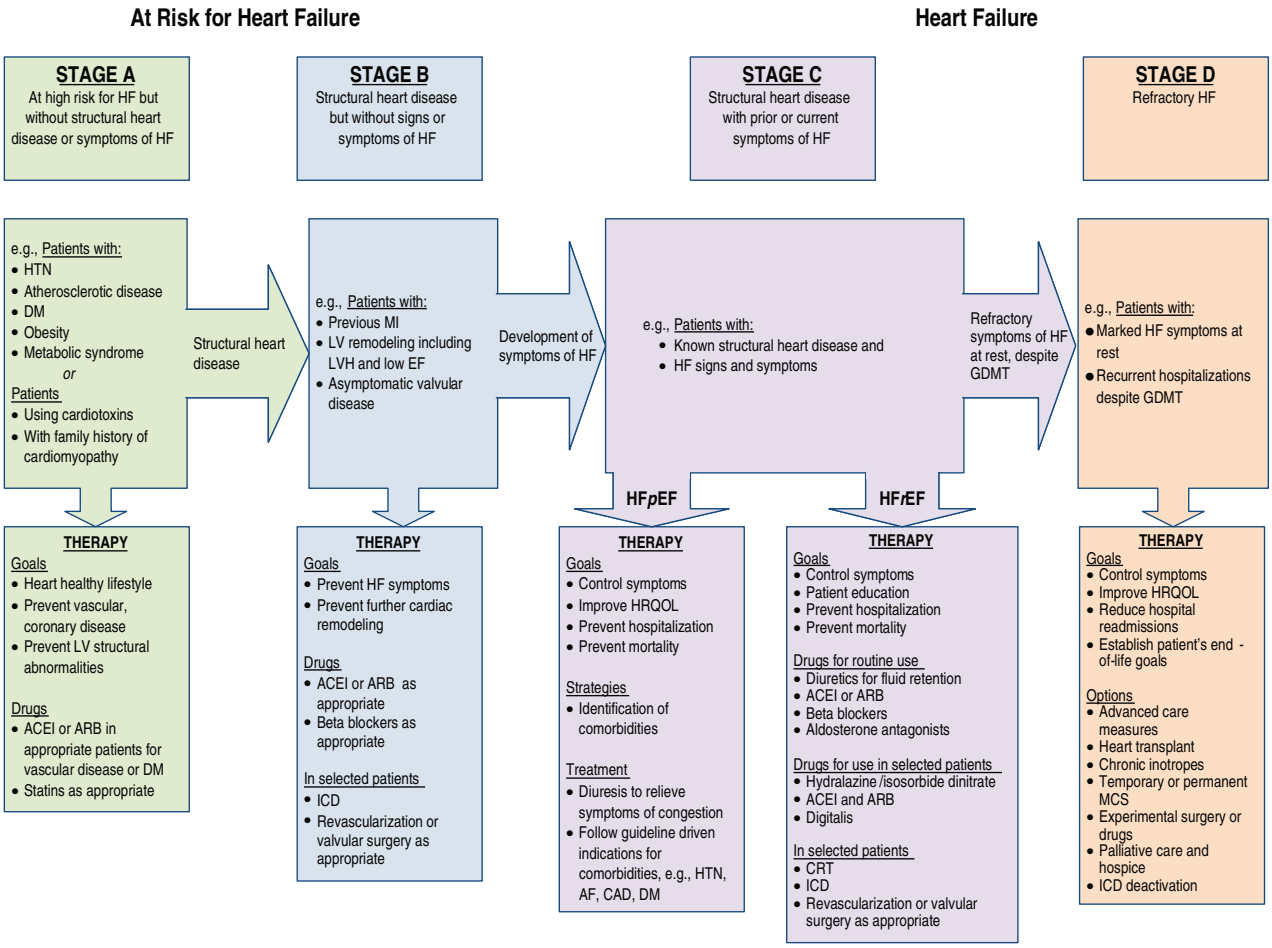


Figure 3. Stages in the development of HF and recommended therapy by stage. ACEI indicates angiotensin-converting enzyme inhibitor; AF, atrial fibrillation; ARB, angiotensin-receptor blocker; CAD, coronary artery disease; CRT, cardiac resynchronization therapy; DM, diabetes mellitus; EF, ejection fraction; GDMT, guideline-directed medical therapy; HF, heart failure; HF*p*EF, heart failure with preserved ejection fraction; HF*r*EF, heart failure with reduced ejection fraction; HRQOL, health-related quality of life; HTN, hypertension; ICD, implantable cardioverter-defibrillator; LV, left ventricular; LVH, left ventricular hypertrophy; MCS, mechanical circulatory support; and MI, myocardial infarction. Adapted from Hunt et al.[38]

8. The Hospitalized Patient

8.1. Classification of Acute Decompensated HF

Hospitalization for HF is a growing and major public health issue.[703] Presently, HF is the leading cause of hospitalization among patients >65 years of age[51]; the largest percentage of expenditures related to HF are directly attributable to hospital costs. Moreover, in addition to costs, hospitalization for acutely decompensated HF represents a sentinel prognostic event in the course of many patients with HF, with a high risk for recurrent hospitalization (eg, 50% at 6 months) and a 1-year mortality rate of approximately 30%.[211,704] The AHA has published a scientific statement about this condition.[705]

There is no widely accepted nomenclature for HF syndromes requiring hospitalization. Patients are described as having "acute HF," "acute HF syndromes," or "acute(ly) decompensated HF"; while the third has gained greatest acceptance, it too has limitations, for it does not make the important distinction between those with a de novo presentation of HF from those with worsening of previously chronic stable HF.

Data from HF registries have clarified the profile of patients with HF requiring hospitalization.[107,704,706,707] Characteristically, such patients are elderly or near elderly, equally male or female, and typically have a history of hypertension, as well as other medical comorbidities, including chronic kidney disease, hyponatremia, hematologic abnormalities, and chronic obstructive pulmonary disease.[107,706,708–713] A relatively equal percentage of patients with acutely decompensated HF have impaired versus preserved LV systolic function[707,714,715]; clinically, patients with preserved systolic function are older, more likely to be female, to have significant hypertension, and to have less CAD. The overall morbidity and mortality for both groups is high.

Hospitalized patients with HF can be classified into important subgroups. These include patients with acute coronary ischemia, accelerated hypertension and acutely decompensated HF, shock, and acutely worsening right HF. Patients who develop HF decompensation after surgical procedures also bear mention. Each of these various categories of HF has specific etiologic factors leading to decompensation, presentation, management, and outcomes.

Noninvasive modalities can be used to classify the patient with hospitalized HF. The history and physical examination allows estimation of a patient's hemodynamic status, that is, the degree of congestion ("dry" versus "wet"), as well as

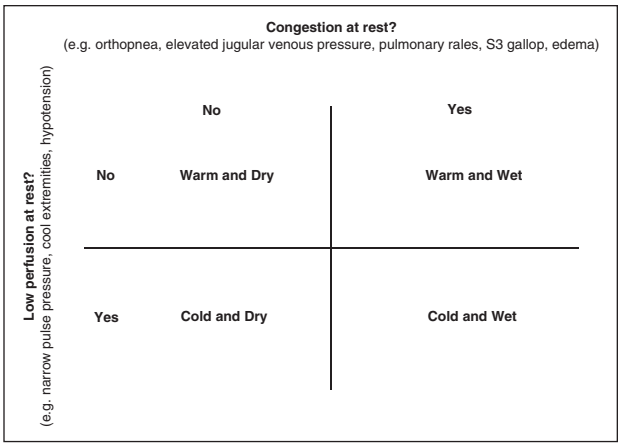


Figure 4. Classification of patients presenting with acutely decompensated heart failure. Adapted with permission from Nohria et al.[716]

the adequacy of their peripheral perfusion ("warm" versus "cold")[716] (Figure 4). Chest x-ray is variably sensitive for the presence of interstitial or alveolar edema, even in the presence of elevated filling pressures. Thus, a normal chest x-ray does not exclude acutely decompensated HF.[717] The utility of natriuretic peptides in patients with acutely decompensated HF has been described in detail in Section 6.3.1. Both BNP and NT-proBNP are useful for the identification or exclusion of acutely decompensated HF in dyspneic patients,[247,249,250,718,719] particularly in the context of uncertain diagnosis.[720–722] Other options for diagnostic evaluation of patients with suspected acutely decompensated HF, such as acoustic cardiography,[723] bioimpedance vector monitoring,[724] or noninvasive cardiac output monitoring[725] are not yet validated.

8.2. Precipitating Causes of Decompensated HF: Recommendations

Class I

1. **ACS precipitating acute HF decompensation should be promptly identified by ECG and serum biomarkers, including cardiac troponin testing, and treated optimally as appropriate to the overall condition and prognosis of the patient.** ***(Level of Evidence: C)***
2. **Common precipitating factors for acute HF should be considered during initial evaluation, as recognition of these conditions is critical to guide appropriate therapy.** ***(Level of Evidence: C)***

ACS is an important cause of worsening or new-onset HF.[726] Although acute ST-segment elevation myocardial infarction can be readily apparent on an ECG, other ACS cases may be more challenging to diagnose. Complicating the clinical scenario is that many patients with acute HF, with or without CAD, have serum troponin levels that are elevated.[727]

However, many other patients may have low levels of detectable troponins not meeting criteria for an acute ischemic event.[278,728] Registry data have suggested that the use of coronary angiography is low for patients hospitalized with decompensated HF, and opportunities to diagnose important CAD may be missed.[729] For the patient with newly discovered HF, clinicians should always consider the possibility that CAD is an underlying cause of HF.[726]

Besides ACS, several other precipitating causes of acute HF decompensation must be carefully assessed to inform appropriate treatment, optimize outcomes, and prevent future acute events in patients with HF.[730] See list below.

Common Factors That Precipitate Acute Decompensated HF

- Nonadherence with medication regimen, sodium and/or fluid restriction
- Acute myocardial ischemia
- Uncorrected high blood pressure
- AF and other arrhythmias
- Recent addition of negative inotropic drugs (eg, verapamil, nifedipine, diltiazem, beta blockers)
- Pulmonary embolus
- Initiation of drugs that increase salt retention (eg, steroids, thiazolidinediones, NSAIDs)
- Excessive alcohol or illicit drug use
- Endocrine abnormalities (eg, diabetes mellitus, hyperthyroidism, hypothyroidism)
- Concurrent infections (eg, pneumonia, viral illnesses)
- Additional acute cardiovascular disorders (eg, valve disease endocarditis, myopericarditis, aortic dissection)

Hypertension is an important contributor to acute HF, particularly among blacks, women, and those with HF*p*EF.[731] In the ADHERE registry, almost 50% of patients admitted with HF had blood pressure >140/90 mm Hg.[107] Abrupt discontinuation of antihypertensive therapy may precipitate worsening HF. The prevalence of AF in patients with acute HF is >30%.[731] Infection increases metabolic demands in general. Pulmonary infections, which are common in patients with HF, may add hypoxia to the increased metabolic demands and are associated with worse outcomes.[730] The sepsis syndrome is associated with reversible myocardial depression that is likely mediated by cytokine release.[732] Patients with HF are hypercoagulable, and the possibility of pulmonary embolus as an etiology of acute decompensation should be considered. Deterioration of renal function can be both a consequence and contributor to decompensated HF. Restoration of normal thyroid function in those with hypothyroidism or hyperthyroidism may reverse abnormal cardiovascular function.[733] In patients treated with amiodarone, thyroid disturbances should be suspected.

Excessive sodium and fluid intake may precipitate acute HF.[379,384] Medication nonadherence for financial or other reasons is a major cause of hospital admission.[734] Several drugs may precipitate acute HF (eg, calcium channel blockers, antiarrhythmic agents, glucocorticoids, NSAIDs and cyclooxygenase-2 inhibitors, thiazolidinediones, and over-the-counter agents like pseudoephedrine). Finally, excessive alcohol intake and use of illicit drugs, such as cocaine and methamphetamine, also need to be investigated as potential causes of HF decompensation.

See Online Data Supplement 37 for additional data on comorbidities in the hospitalized patient.

8.3. Maintenance of GDMT During Hospitalization: Recommendations

Class I

1. **In patients with HF*r*EF experiencing a symptomatic exacerbation of HF requiring hospitalization during chronic maintenance treatment with GDMT, it is recommended that GDMT be continued in the absence of hemodynamic instability or contraindications.[195,735,736] *(Level of Evidence: B)***
2. **Initiation of beta-blocker therapy is recommended after optimization of volume status and successful discontinuation of intravenous diuretics, vasodilators, and inotropic agents. Beta-blocker therapy should be initiated at a low dose and only in stable patients. Caution should be used when initiating beta blockers in patients who have required inotropes during their hospital course.[195,735,736] *(Level of Evidence: B)***

The patient's maintenance HF medications should be carefully reviewed on admission, and it should be decided whether adjustments should be made as a result of the hospitalization. In the majority of patients with HF*r*EF who are admitted to the hospital, oral HF therapy should be continued, or even uptitrated, during hospitalization. It has been demonstrated that continuation of ACE inhibitors or ARBs and beta blockers for most patients is well tolerated and results in better outcomes.[195,735,736] Withholding of, or reduction in, beta-blocker therapy should be considered only in patients hospitalized after recent initiation or increase in beta-blocker therapy or with marked volume overload or marginal/low cardiac output. Patients admitted with significant worsening of renal function should be considered for a reduction in, or temporary discontinuation of ACE inhibitors, ARBs, and/or aldosterone antagonists until renal function improves. Although it is important to ensure that evidence-based medications are instituted before hospital discharge, it is equally critical to reassess medications on admission and adjust their administration in light of the worsening HF.

8.4. Diuretics in Hospitalized Patients: Recommendations

Class I

1. **Patients with HF admitted with evidence of significant fluid overload should be promptly treated with intravenous loop diuretics to reduce morbidity.[737,738] *(Level of Evidence: B)***
2. **If patients are already receiving loop diuretic therapy, the initial intravenous dose should equal or exceed their chronic oral daily dose and should be given as either intermittent boluses or continuous infusion. Urine output and signs and symptoms of congestion should be serially assessed, and the diuretic dose should be adjusted accordingly to relieve symptoms, reduce volume excess, and avoid hypotension.[739] *(Level of Evidence: B)***
3. **The effect of HF treatment should be monitored with careful measurement of fluid intake and output, vital signs, body weight that is determined at the same time each day, and clinical signs and symptoms of systemic perfusion and congestion. Daily serum electrolytes, urea nitrogen, and creatinine concentrations should be measured during the use of intravenous diuretics or active titration of HF medications. *(Level of Evidence: C)***

Class IIa

1. **When diuresis is inadequate to relieve symptoms, it is reasonable to intensify the diuretic regimen using either:**
   a. **higher doses of intravenous loop diuretics[38,739] *(Level of Evidence: B)*; or**
   b. **addition of a second (eg, thiazide) diuretic.[740–743] *(Level of Evidence: B).***

Class IIb

1. **Low-dose dopamine infusion may be considered in addition to loop diuretic therapy to improve diuresis and better preserve renal function and renal blood flow.[744,745] *(Level of Evidence: B)***

Patients with significant fluid overload should be initially treated with loop diuretics given intravenously during hospitalization. Therapy should begin in the emergency department without delay, as early therapy has been associated with better outcomes.[37,738] Patients should be carefully monitored, including serial evaluation of volume status and systemic perfusion. Monitoring of daily weight, supine and standing vital signs, and fluid input and output is necessary for daily management. Assessment of daily electrolytes and renal function should be performed while intravenous diuretics are administered or HF medications are actively titrated. Intravenous loop diuretics have the potential to reduce glomerular filtration rate, further worsen neurohumoral activation, and produce electrolyte disturbances. Thus, although the use of diuretics may relieve symptoms, their impact on mortality has not been well studied. Diuretics should be administered at doses sufficient to achieve optimal volume status and relieve congestion without inducing an excessively rapid reduction in intravascular volume, which could result in hypotension, renal dysfunction, or both. Because loop diuretics have a relatively short half-life, sodium reabsorption in the tubules will occur once the tubular concentration of the diuretics declines. Therefore, limiting sodium intake and dosing the diuretic continuously or multiple times per day will enhance diuretic effectiveness.[434,737,746–748]

Some patients may present with moderate to severe renal dysfunction such that the diuretic response may be blunted, necessitating higher initial diuretic doses. In many cases, reduction of fluid overload may improve congestion and improve renal function, particularly if significant venous congestion is reduced.[749] Clinical experience suggests it is difficult to determine whether congestion has been adequately treated in many patients, and registry data have confirmed that patients are frequently discharged after a net weight loss of only a few pounds. Although patients may rapidly improve symptomatically, they may remain congested or hemodynamically compromised. Routine use of serial natriuretic peptide measurement or Swan-Ganz catheter has not been conclusively shown to improve outcomes among these patients. Nevertheless, careful evaluation of all physical findings, laboratory parameters, weight change, and net fluid change should be considered before discharge.

When a patient does not respond to initial intravenous diuretics, several options may be considered. Efforts should be made to

make certain that congestion persists and that another hemodynamic profile or alternate disease process is not evident. If there is doubt about the fluid status, consideration should be given for assessment of filling pressures and cardiac output using right-heart catheterization. If volume overload is confirmed, the dose of the loop diuretic should be increased to ensure that adequate drug levels reach the kidney. Adding a second diuretic, typically a thiazide, can improve diuretic responsiveness.[435,442,443] Theoretically, continuous diuretic infusion may enhance diuresis because continuous diuretic delivery to the nephron avoids rebound sodium and fluid reabsorption.[440,441,750,751] However, the DOSE (Diuretic Optimization Strategies Evaluation) trial did not find any significant difference between continuous infusion versus intermittent bolus strategies for symptoms, diuresis, or outcomes.[739] It is reasonable to try an alternate approach of using either bolus or continuous infusion therapy different from the initial strategy among patients who are resistant to diuresis. Finally, some data suggest that low-dose dopamine infusion in addition to loop diuretics may improve diuresis and better preserve renal function, although ongoing trials will provide further data on this effect.[744]

See Online Data Supplement 17 for additional data on diuretics.

8.5. Renal Replacement Therapy—Ultrafiltration: Recommendations

Class IIb

1. **Ultrafiltration may be considered for patients with obvious volume overload to alleviate congestive symptoms and fluid weight.[752] *(Level of Evidence: B)***
2. **Ultrafiltration may be considered for patients with refractory congestion not responding to medical therapy. *(Level of Evidence: C)***

If all diuretic strategies are unsuccessful, ultrafiltration may be considered. Ultrafiltration moves water and small- to medium-weight solutes across a semipermeable membrane to reduce volume overload. Because the electrolyte concentration is similar to plasma, relatively more sodium can be removed than by diuretics.[753–755] Initial studies supporting use of ultrafiltration in HF were small but provided safety and efficacy data in acute HF.[755–757] Use of ultrafiltration in HF has been shown to reduce neurohormone levels and increase diuretic responsiveness. In a larger trial of 200 unselected patients with acute HF, ultrafiltration did reduce weight compared with bolus or continuous diuretics at 48 hours, had similar effects on the dyspnea score compared with diuretics, and improved readmission rate at 90 days.[752] A randomized acute HF trial in patients with cardiorenal syndrome and persistent congestion has failed to demonstrate a significant advantage of ultrafiltration over bolus diuretic therapy.[758,759] Cost, the need for veno-venous access, provider experience, and nursing support remain concerns about the routine use of ultrafiltration. Consultation with a nephrologist is appropriate before initiating ultrafiltration, especially in circumstances where the non-nephrology provider does not have sufficient experience with ultrafiltration.

See Online Data Supplements 17 and 38 for additional data on diuretics versus ultrafiltration in acute decompensated HF and worsening renal function and mortality.

8.6. Parenteral Therapy in Hospitalized HF: Recommendation

Class IIb

1. **If symptomatic hypotension is absent, intravenous nitroglycerin, nitroprusside, or nesiritide may be considered an adjuvant to diuretic therapy for relief of dyspnea in patients admitted with acutely decompensated HF.[760–763] *(Level of Evidence: A)***

The different vasodilators include 1) intravenous nitroglycerin, 2) sodium nitroprusside, and 3) nesiritide.

Intravenous nitroglycerin acts primarily through venodilation, lowers preload, and may help to rapidly reduce pulmonary congestion.[764,765] Patients with HF and hypertension, coronary ischemia, or significant mitral regurgitation are often cited as ideal candidates for the use of intravenous nitroglycerin. However, tachyphylaxis to nitroglycerin may develop within 24 hours, and up to 20% of those with HF may develop resistance to even high doses.[766–768]

Sodium nitroprusside is a balanced preload-reducing venodilator and afterload-reducing arteriodilator that also dilates the pulmonary vasculature.[769] Data demonstrating efficacy are limited, and invasive hemodynamic blood pressure monitoring (such as an arterial line) is typically required; in such cases, blood pressure and volume status should be monitored frequently. Nitroprusside has the potential for producing marked hypotension and is usually used in the intensive care setting as well; longer infusions of the drug have been rarely associated with thiocyanate toxicity, particularly in the setting of renal insufficiency. Nitroprusside is potentially of value in severely congested patients with hypertension or severe mitral valve regurgitation complicating LV dysfunction.

Nesiritide (human BNP) reduces LV filling pressure but has variable effects on cardiac output, urinary output, and sodium excretion. An initial study demonstrated that the severity of dyspnea is reduced more rapidly compared with diuretics alone.[760] A large randomized trial in patients with acute decompensated HF demonstrated nesiritide had no impact on mortality, rehospitalization, or renal function, a small but statistically significant impact on dyspnea, and an increased risk of hypotension.[762] Because nesiritide has a longer effective half-life than nitroglycerin or nitroprusside, adverse effects such as hypotension may persist longer. Overall, presently there are no data that suggest that intravenous vasodilators improve outcomes in the patient hospitalized with HF; as such, use of intravenous vasodilators is limited to the relief of dyspnea in the hospitalized HF patient with intact blood pressure. Administration of intravenous vasodilators in patients with HF*p*EF should be done with caution because these patients are typically more volume sensitive.

The use of inotropic support as indicated for hospitalized HF with shock or impending shock and/or end-organ perfusion limitations is addressed in Section 7.4.4. See Table 26 for drug therapies and *Online Data Supplements 32 and 33* for additional information on inotropic support.

See Online Data Supplement 39 for additional data on nesiritide.

8.7. Venous Thromboembolism Prophylaxis in Hospitalized Patients: Recommendation

Class I

1. **A patient admitted to the hospital with decompensated HF should receive venous thromboembolism prophylaxis with an anticoagulant medication if the risk–benefit ratio is favorable.[21,770] *(Level of Evidence: B)***

HF has long been recognized as affording additional risk for venous thromboembolic disease, associated with a number of pathophysiologic changes, including reduced cardiac output, increased systemic venous pressure, and chemical changes promoting blood clotting. When patients are hospitalized for decompensated HF or when patients with chronic stable HF are hospitalized for other reasons, they are at increased risk for venous thromboembolic disease, although accurate numerical estimates are lacking in the literature.

Most early data on the effectiveness of different anticoagulant regimens to reduce the incidence of venous thromboembolic disease in hospitalized patients were either observational, retrospective reports[776,777] or prospective studies using a variety of drugs and differing definitions of therapeutic effect and endpoints,[774,778–780] making summary conclusions difficult. Early studies involved patients with far longer hospital lengths of stay than occur presently and were performed well before present standard-of-care treatments and diagnostic tests were available.[774,778–780] Newer trials using presently available antithrombotic drugs often were not limited to patients with HF but included those with other acute illnesses, severe respiratory diseases, or simply a broad spectrum of hospitalized medical patients.[771–774,781] In most studies, patients were categorized as having HF by admitting diagnosis, clinical signs, or functional class, whereas only 1 study[782] provided LVEF data on enrolled study patients. All included trials tried to exclude patients perceived to have an elevated risk of bleeding complications or with an elevated risk of toxicity from the specific agent tested (eg, enoxaparin in patients with compromised renal function). Patients with HF typically made up a minority of the study cohort, and significance of results were not always reported by the authors, making ACCF/AHA class I recommendations difficult to support using this guideline methodology. In some trials, concurrent aspirin was allowed but not controlled for as a confounding variable.[772,783]

For patients admitted specifically for decompensated HF and with adequate renal function (serum creatinine <2.0 mg/dL), randomized trials suggest that enoxaparin 40 mg subcutaneously once daily[770,773,774,783] or unfractionated heparin 5000 units subcutaneously every 8 hours[771] will reduce radiographically demonstrable venous thrombosis. Effects on mortality or clinically significant pulmonary embolism rates are unclear. Lower doses of enoxaparin do not appear superior to placebo,[770,773] whereas continuing weight-based enoxaparin therapy up to 3 months after hospital discharge does not appear to provide additional benefit.[782]

A single prospective study failed to demonstrate certoparin to be noninferior to unfractionated heparin,[783] whereas retrospective analysis of a prospective trial of dalteparin was underpowered to determine benefit in its HF cohort.[776] Fondaparinux failed to show significant difference from placebo in an RCT that included a subgroup of 160 patients with HF.[781]

No adequate trials have evaluated anticoagulant benefit in patients with chronic but stable HF admitted to the hospital for other reasons. However, the MEDENOX (Medical Patients with Enoxaparin) trial suggested that the benefit of enoxaparin may extend to this population.[770,773,774]

A systematic review[784] failed to demonstrate prophylactic efficacy of graded compression stockings in general medical patients, but significant cutaneous complications were associated with their use. No studies were performed exclusively on patients with HF. Two RCTs in patients with stroke found no efficacy of these devices.[785,786]

See Online Data Supplement 20 for additional data on anticoagulation.

8.8. Arginine Vasopressin Antagonists: Recommendation

Class IIb

1. **In patients hospitalized with volume overload, including HF, who have persistent severe hyponatremia and are at risk for or having active cognitive symptoms despite water restriction and maximization of GDMT, vasopressin antagonists may be considered in the short term to improve serum sodium concentration in hypervolemic, hyponatremic states with either a V_2 receptor selective or a nonselective vasopressin antagonist.[787,788] *(Level of Evidence: B)***

Even mild hyponatremia may be associated with neurocognitive problems, including falls and attention deficits.[789] Treatment of hypervolemic hyponatremia with a V_2-selective vasopressin antagonist (tolvaptan) was associated with a significant improvement in the mental component of the Medical Outcomes Study Short Form General Health Survey.[788] Hyponatremia may be treated with water restriction and maximization of GDMT that modulate angiotensin II, leading to improved renal perfusion and decreased thirst. Alternative causes of hyponatremia (eg, syndrome of inappropriate antidiuretic hormone, hypothyroidism, and hypoaldosteronism) should be assessed. Vasopressin antagonists improve serum sodium in hypervolemic, hyponatremic states[787,788]; however, longer-term therapy with a V_2-selective vasopressin antagonist did not improve mortality in patients with HF.[790,791] Currently, 2 vasopressin antagonists are available for clinical use: conivaptan and tolvaptan. It may be reasonable to use a nonselective vasopressin antagonist to treat hyponatremia in patients with HF with cognitive symptoms due to hyponatremia. However, the long-term safety and benefit of this approach remains unknown. A summary of the recommendations for the hospitalized patient appears in Table 28.

8.9. Inpatient and Transitions of Care: Recommendations

See Table 29 for a summary of recommendations from this section.

Class I

1. **The use of performance improvement systems and/or evidence-based systems of care is recommended in the hospital and early postdischarge outpatient setting to**

identify appropriate HF patients for GDMT, provide clinicians with useful reminders to advance GDMT, and assess the clinical response.[82,365,706,792–796] *(Level of Evidence: B)*

2. Throughout the hospitalization as appropriate, before hospital discharge, at the first postdischarge visit, and in subsequent follow-up visits, the following should be addressed.[204,795,797–799] *(Level of Evidence: B)*:
   a. initiation of GDMT if not previously established and not contraindicated;
   b. precipitant causes of HF, barriers to optimal care transitions, and limitations in postdischarge support;

Table 28. Recommendations for Therapies in the Hospitalized HF Patient

Recommendations	COR	LOE	References
HF patients hospitalized with fluid overload should be treated with intravenous diuretics	I	B	737, 738
HF patients receiving loop diuretic therapy should receive an initial parenteral dose greater than or equal to their chronic oral daily dose; then dose should be serially adjusted	I	B	739
HFrEF patients requiring HF hospitalization on GDMT should continue GDMT except in cases of hemodynamic instability or where contraindicated	I	B	195, 735, 736
Initiation of beta-blocker therapy at a low dose is recommended after optimization of volume status and discontinuation of intravenous agents	I	B	195, 735, 736
Thrombosis/thromboembolism prophylaxis is recommended for patients hospitalized with HF	I	B	21, 770–774
Serum electrolytes, urea nitrogen, and creatinine should be measured during titration of HF medications, including diuretics	I	C	N/A
When diuresis is inadequate, it is reasonable to	IIa		
a. give higher doses of intravenous loop diuretics; or		B	38, 739
b. add a second diuretic (eg, thiazide)		B	740–743
Low-dose dopamine infusion may be considered with loop diuretics to improve diuresis	IIb	B	744, 745
Ultrafiltration may be considered for patients with obvious volume overload	IIb	B	752
Ultrafiltration may be considered for patients with refractory congestion	IIb	C	N/A
Intravenous nitroglycerin, nitroprusside, or nesiritide may be considered an adjuvant to diuretic therapy for stable patients with HF	IIb	A	760–763
In patients hospitalized with volume overload and severe hyponatremia, vasopressin antagonists may be considered	IIb	B	787, 788

COR indicates Class of Recommendation; GDMT, guideline-directed medical therapy; HF, heart failure; HFrEF, heart failure with reduced ejection fraction; LOE, Level of Evidence; and N/A, not available.

Table 29. Recommendations for Hospital Discharge

Recommendations or Indications	COR	LOE	References
Performance improvement systems in the hospital and early postdischarge outpatient setting to identify HF for GDMT	I	B	82, 365, 706, 792–796
Before hospital discharge, at the first postdischarge visit, and in subsequent follow-up visits, the following should be addressed: a. initiation of GDMT if not done or contraindicated; b. causes of HF, barriers to care, and limitations in support; c. assessment of volume status and blood pressure with adjustment of HF therapy; d. optimization of chronic oral HF therapy; e. renal function and electrolytes; f. management of comorbid conditions; g. HF education, self-care, emergency plans, and adherence; and h. palliative or hospice care	I	B	204, 795, 797–799
Multidisciplinary HF disease-management programs for patients at high risk for hospital readmission are recommended	I	B	82, 800–802
A follow-up visit within 7 to 14 d and/or a telephone follow-up within 3 d of hospital discharge are reasonable	IIa	B	101, 803
Use of clinical risk-prediction tools and/or biomarkers to identify higher-risk patients are reasonable	IIa	B	215

COR indicates Class of Recommendation; GDMT, guideline-directed medical therapy; HF, heart failure; and LOE, Level of Evidence.

c. **assessment of volume status and supine/upright hypotension with adjustment of HF therapy as appropriate;**
d. **titration and optimization of chronic oral HF therapy;**
e. **assessment of renal function and electrolytes where appropriate;**
f. **assessment and management of comorbid conditions;**
g. **reinforcement of HF education, self-care, emergency plans, and need for adherence; and**
h. **consideration for palliative care or hospice care in selected patients.**

3. **Multidisciplinary HF disease-management programs are recommended for patients at high risk for hospital readmission, to facilitate the implementation of GDMT, to address different barriers to behavioral change, and to reduce the risk of subsequent rehospitalization for HF.[82,800–802] *(Level of Evidence: B)***

Class IIa

1. **Scheduling an early follow-up visit (within 7 to 14 days) and early telephone follow-up (within 3 days) of hospital discharge are reasonable.[101,803] *(Level of Evidence: B)***
2. **Use of clinical risk-prediction tools and/or biomarkers to identify patients at higher risk for postdischarge clinical events are reasonable.[215] *(Level of Evidence: B)***

Decisions about pharmacological therapies delivered during hospitalization likely can impact postdischarge outcome. Continuation or initiation of HF GDMT prior to hospital discharge is associated with substantially improved clinical outcomes for patients with HF*r*EF. However, caution should be used when initiating beta blockers in patients who have required inotropes during their hospital course or when initiating ACE inhibitors, ARBs, or aldosterone antagonists in those patients who have experienced marked azotemia or are at risk for hyperkalemia. The patient should be transitioned to oral diuretic therapy to verify its effectiveness. Similarly, optimal volume status should be achieved. Blood pressure should be adequately controlled, and, in patients with AF, ventricular response should also be well controlled. The hospitalization is a "teachable moment" to reinforce patient and family education and develop a plan of care, which should be communicated to the appropriate healthcare team.

Safety for patients hospitalized with HF is crucial. System changes necessary to achieve safer care include the adoption by all US hospitals of a standardized set of 30 "Safe Practices" endorsed by the National Quality Forum[804] and National Patient Safety Goals espoused by The Joint Commission.[805] Improved communication between clinicians and nurses, medication reconciliation, carefully planned transitions between care settings, and consistent documentation are examples of patient safety standards that should be ensured for patients with HF discharged from the hospital.

The prognosis of patients hospitalized with HF, and especially those with serial readmissions, is suboptimal. Hence, appropriate levels of symptomatic relief, support, and palliative care for patients with chronic HF should be addressed as an ongoing key component of the plan of care, especially when patients are hospitalized with acute decompensation.[806] The appropriateness of discussion about advanced therapy or end-of-life preferences is reviewed in Section 11.

For patients with HF, the transition from inpatient to outpatient care can be an especially vulnerable period because of the progressive nature of the disease state, complex medical regimens, the large number of comorbid conditions, and the multiple clinicians who may be involved. Patient education and written discharge instructions or educational material given to the patient, family members, and/or caregiver during the hospital stay or at discharge to home are essential components of transition care. These should address all of the following: activity level, diet, discharge medications, follow-up appointment, weight monitoring, and what to do if symptoms worsen.[297] Thorough discharge planning that includes special emphasis on ensuring adherence to an evidence-based medication regimen[795] is associated with improved patient outcomes.[792,797,807] More intensive delivery of discharge instructions, coupled tightly with subsequent well-coordinated follow-up care for patients hospitalized with HF, has produced positive results in several studies.[82,793,800] The addition of a 1-hour, nurse educator–delivered teaching session at the time of hospital discharge, using standardized instructions, resulted in improved clinical outcomes, increased self-care and treatment adherence, and reduced cost of care. Patients receiving the education intervention also had a lower risk of rehospitalization or death and lower costs of care.[365] There are ongoing efforts to further develop evidence-based interventions in this population.

Transitional care extends beyond patient education. Care information, especially changes in orders and new diagnostic information, must be transmitted in a timely and clearly understandable form to all of the patient's clinicians who will be delivering follow-up care. Other important components of transitional care include preparation of the patient and caregiver for what to expect at the next site of care, reconciliation of medications, follow-up plans for outstanding tests, and discussions about monitoring signs and symptoms of worsening conditions. Early outpatient follow-up, a central element of transitional care, varies significantly across US hospitals. Early postdischarge follow-up may help minimize gaps in understanding of changes to the care plan or knowledge of test results and has been associated with a lower risk of subsequent rehospitalization.[803] A follow-up visit within 7 to 14 days and/or a telephone follow-up within 3 days of hospital discharge are reasonable goals of care.

See Online Data Supplement 40 for additional data on oral medications for the hospitalized patient.

9. Important Comorbidities in HF

9.1. Atrial Fibrillation§

Patients with HF are more likely than the general population to develop AF.[808] There is a direct relationship between the NYHA class and prevalence of AF in patients with HF progressing from 4% in those who are NYHA class I to 40% in those who are NYHA class IV.[809] AF is also a strong independent risk factor for subsequent development of HF.[376,808] In addition to those

§The "ACC/AHA/ESC 2006 Guidelines for the Management of Patients With Atrial Fibrillation" and the 2 subsequent focused updates from 2011[6–8] are considered policy at the time of publication of the present HF Guideline; however, a fully revised AF guideline, which will include updated recommendations on AF, is in development, with publication expected in 2013 or 2014.

Table 30. Clinical Evaluation in Patients With AF

Minimum evaluation	
1. History and physical examination, to define	• Presence and nature of symptoms associated with AF • Clinical type of AF (paroxysmal, persistent, or permanent) • Onset of first symptomatic attack or date of discovery of AF • Frequency, duration, precipitating factors, and modes of termination of AF • Response to any pharmacological agents that have been administered • Presence of any underlying heart disease or other reversible conditions (eg, hyperthyroidism or alcohol consumption)
2. ECG, to identify	• Rhythm (verify AF) • LV hypertrophy • P-wave duration and morphology or fibrillatory waves • Preexcitation • Bundle-branch block • Prior MI • Other atrial arrhythmias • To measure and follow the R-R, QRS, and QT intervals in conjunction with antiarrhythmic drug therapy
3. Transthoracic echocardiogram, to identify	• Valvular heart disease • LA and RA size • LV and RV size and function • Peak RV pressure (pulmonary hypertension) • LV hypertrophy • LA thrombus (low sensitivity) • Pericardial disease
4. Blood tests of thyroid, renal, and hepatic function	• For a first episode of AF, when the ventricular rate is difficult to control
Additional testing (one or several tests may be necessary)	
1. 6-Minute walk test	• If the adequacy of rate control is in question
2. Exercise testing	• If the adequacy of rate control is in question (permanent AF) • To reproduce exercise-induced AF • To exclude ischemia before treatment of selected patients with a type IC antiarrhythmic drug
3. Holter monitoring or event recording	• If diagnosis of the type of arrhythmia is in question • As a means of evaluating rate control
4. Transesophageal echocardiography	• To identify LA thrombus (in the LA appendage) • To guide cardioversion
5. Electrophysiological study	• To clarify the mechanism of wide-QRS-complex tachycardia • To identify a predisposing arrhythmia such as atrial flutter or paroxysmal supraventricular tachycardia • To seek sites for curative ablation or AV conduction block/modification
6. Chest x-ray to evaluate	• Lung parenchyma, when clinical findings suggest an abnormality • Pulmonary vasculature, when clinical findings suggest an abnormality

Type IC refers to the Vaughan Williams classification of antiarrhythmic drugs.

AF indicates atrial fibrillation; AV, atrioventricular; ECG, electrocardiogram; LA, left atrial; LV, left ventricular; MI, myocardial infarction; RA, right atrial; and RV, right ventricular.

Reproduced from Fuster et al.[6]

with HF*r*EF, patients with HF*p*EF are also at greater risk for AF than the general age-matched population.[811] HF and AF can interact to promote their perpetuation and worsening through mechanisms such as rate-dependent worsening of cardiac function, fibrosis, and activation of neurohumoral vasoconstrictors. AF can worsen symptoms in patients with HF, and, conversely, worsened HF can promote a rapid ventricular response in AF.

Similar to other patient populations, for those with AF and HF, the main goals of therapy are prevention of thromboembolism and symptom control. Most patients with AF and HF would be expected to be candidates for systemic anticoagulation unless otherwise contraindicated. General principles of management include correction of underlying causes of AF and HF as well as optimization of HF management (Table 30). As in other patient populations, the issue of rate control versus rhythm control has been investigated. For patients who develop HF as a result of AF, a rhythm control strategy should be pursued. It is important to recognize that AF with a rapid ventricular response is one of the few potentially reversible causes of HF. Because of this, a patient who presents with newly detected HF in the presence of AF with a rapid ventricular response should be presumed to have a rate-related cardiomyopathy until proved otherwise. In this situation, 2 strategies can be considered. One is rate control of the patient's AF and see if HF and EF improve. The other is to try to restore and maintain sinus rhythm. In this situation, it is common practice to initiate amiodarone and then arrange for cardioversion 1 month later. Amiodarone has the advantage of being both an effective rate-control medication and the most effective antiarrhythmic medication with a lower risk of proarrhythmic effect.

In patients with HF who develop AF, a rhythm-control strategy has not been shown to be superior to a rate-control strategy.[812] If rhythm control is chosen, limited data suggest that AF catheter ablation in HF patients may lead to improvement in LV function and quality of life but is less likely to be effective than in patients with intact cardiac function.[813,814] Because of their favorable effect on morbidity and mortality in patients with systolic HF, beta-adrenergic blockers are the preferred agents for achieving rate control unless otherwise contraindicated.

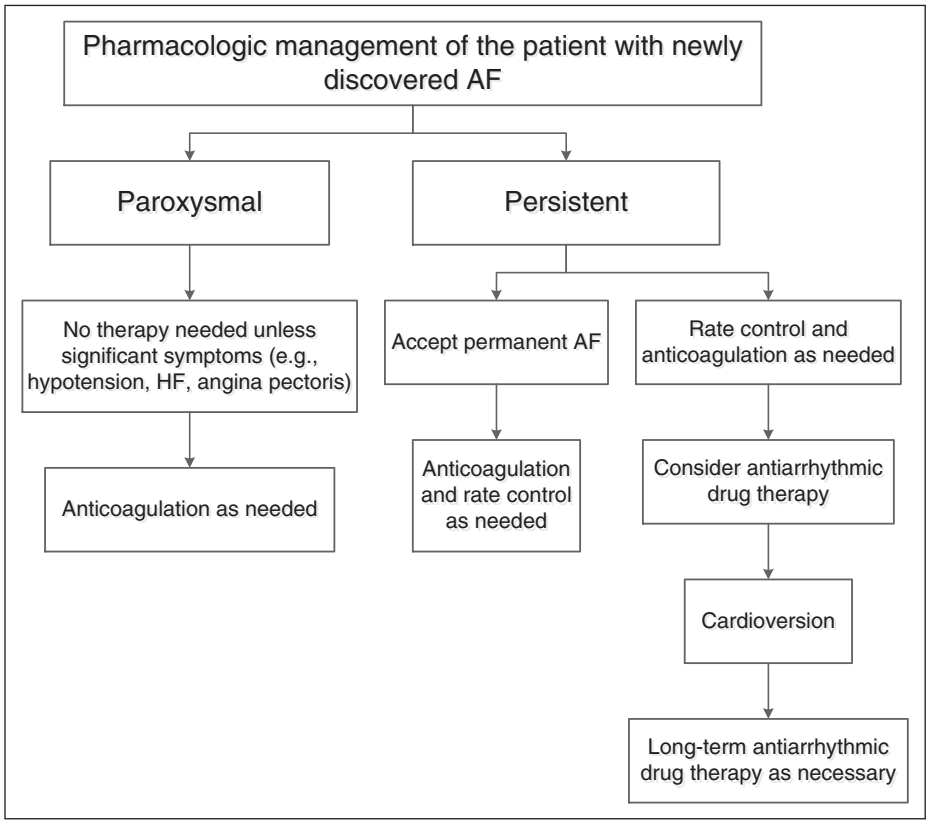


Figure 5. Pharmacological management of patients with newly discovered AF. AF indicates atrial fibrillation; and HF, heart failure. Reproduced from Fuster et al.[6]

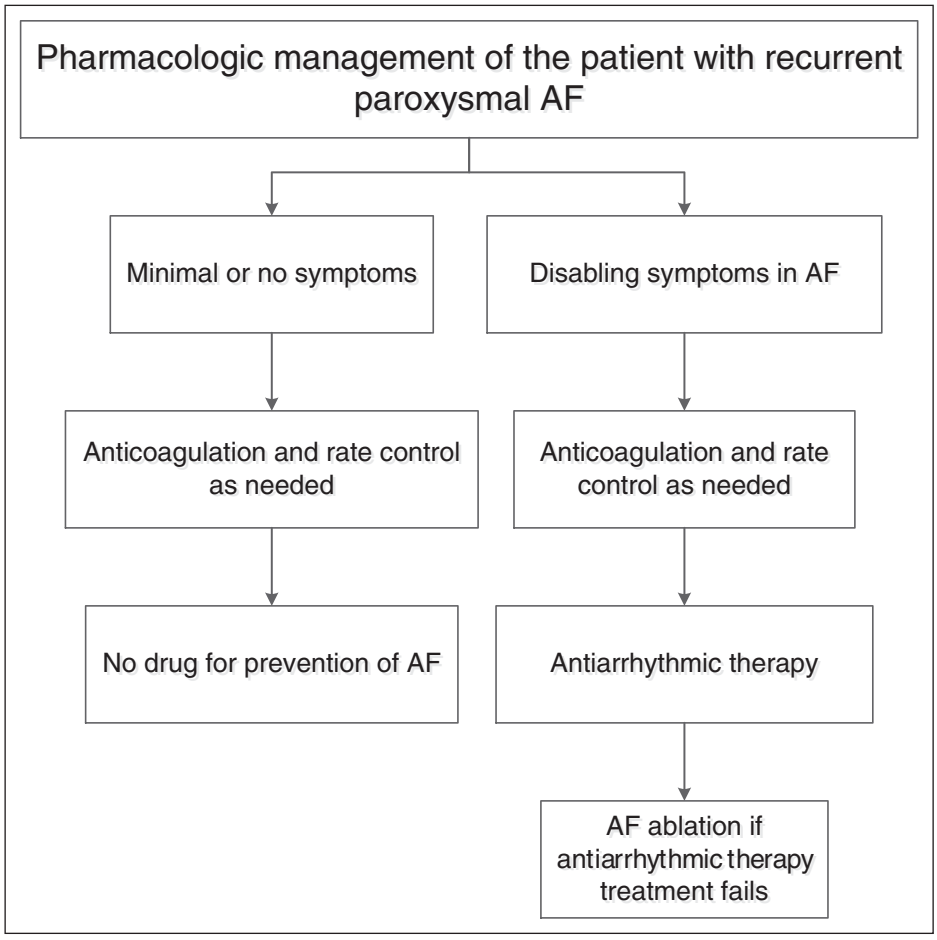


Figure 6. Pharmacological management of patients with recurrent paroxysmal AF. AF indicates atrial fibrillation. Reproduced from Fuster et al.[6]

Digoxin may be an effective adjunct to a beta blocker. The nondihydropyridine calcium antagonists, such as diltiazem, should be used with caution in those with depressed EF because of their negative inotropic effect. For those with HF*p*EF, nondihydropyridine calcium antagonists can be effective for achieving rate control but may be more effective when used in combination with digoxin. For those for whom a rate-control strategy is chosen, when rate control cannot be achieved either because of drug inefficacy or intolerance, atrioventricular node ablation and CRT device placement can be useful.[78,116,595,596] See Figures 5 and 6 for AF treatment algorithms.

See Online Data Supplement 41 for additional data on AF.

9.2. Anemia

Anemia is a common finding in patients with chronic HF. Although variably reported, in part due to the lack of consensus on the definition of anemia, the prevalence of anemia among patients with HF increases with HF severity. Anemia is also more common in women and is seen in both patients with HF*r*EF and HF*p*EF.[818–823] The World Health Organization defines anemia as a hemoglobin level of <12 g/dL in women and <13 g/dL in men. Registries have reported anemia to be present in 25% to 40% of HF patients.[818–820] Anemia is associated with an increased mortality risk in HF. In a large study of >150,000 patients, the mortality risk was approximately doubled in anemic HF patients compared with those without anemia, and this risk persisted after controlling for other confounders, including renal dysfunction and HF severity.[818] Anemia is also associated with reduced exercise capacity, impaired HRQOL, and a higher risk for hospitalization.[225,819,824,825] These risks are inversely and linearly associated with hemoglobin levels, although a U-shaped risk with the highest hemoglobin levels has been reported.[822,826]

Multiple etiological factors, many of which coexist within individual patients, contribute to the development of anemia in HF. Anemia in patients with HF is often normocytic and accompanied by an abnormally low reticulocyte count.[825,827] Evaluation of anemia in HF requires careful consideration of other causes, the most common being secondary causes of iron deficiency anemia.

In persons without identifiable causes of anemia, erythropoiesis-stimulating agents have gained significant interest as potential adjunctive therapy in the patient with HF. In a retrospective study of erythropoiesis-stimulating agents in 26 patients with HF and anemia, the hemoglobin level, LVEF, and functional class improved.[828] These patients required lower diuretic doses and were hospitalized less often. Similar findings were also observed in a randomized open-label study of 32 patients.[829] A single-blind RCT showed that erythropoietin increased hemoglobin, peak oxygen uptake, and exercise duration in patients with severe HF and anemia.[830] Two further studies confirmed these findings; however, none of these were double blind.[831,832]

These positive data led to 2 larger studies. A 165-patient study showed that darbepoetin alfa was associated with improvement in several HRQOL measures with a trend toward improved exercise capacity (6-minute walking distance +34±7 m versus +11±10 m, P=0.074).[833] In STAMINA-HeFT (Study of Anemia in Heart Failure Trial), 319 patients were randomly assigned to darbepoetin alfa or placebo for 12 months.[834] Although darbepoetin alfa did not improve exercise duration, it was well tolerated, and a trend toward improvement in the composite endpoint of all-cause mortality or first hospitalization for HF was seen (hazard ratio: 0.68; 95% confidence interval: 0.43 to 1.08; P=0.10).[834] These favorable data led to the design and initiation of the RED-HF (Phase III Reduction of Events With Darbepoetin alfa in Heart Failure) trial.[835]

Two trials in erythropoiesis-stimulating agents, however, later raised concerns that patients treated with an erythropoiesis-stimulating agent may have an increased risk of cardiovascular events.[836,837] Because the populations in these trials differed, the RED-HF trial was continued. Nevertheless, at the completion of the trial, the investigators concluded that treatment with darbepoetin alfa did not improve clinical outcomes in patients with systolic HF and mild-to-moderate anemia.[838] Finally, a trial using intravenous iron as a supplement in patients with HF*r*EF with iron deficiency showed an improvement in functional status.[840] There were no untoward adverse effects of iron in this trial. In the absence of a definitive evidence base, the writing committee has deferred a specific treatment recommendation regarding anemia.

9.3. Depression

Depression is common in patients with HF; those with depressive symptoms have lower HRQOL, poorer self-care, worse clinical outcomes, and more use of healthcare services.[841–843] Although it might be assumed that depression occurs only among hospitalized patients,[844] a multicenter study demonstrated that even at least 3 months after a hospitalization, 63% of patients with HF reported symptoms of depression.[845] Potential pathophysiologic mechanisms proposed to explain the high prevalence of depression in HF include autonomic nervous system dysfunction, inflammation, cardiac arrhythmias, and altered platelet function, but the mechanism remains unclear.[846] Although remission from depression may improve cardiovascular outcomes, the most effective intervention strategy is not yet known.[842]

9.4. Other Multiple Comorbidities

Although there are additional and important comorbidities that afflict patients with HF as shown in Table 31, how best to generate specific recommendations remains uncertain, given the status of current evidence.

10. Surgical/Percutaneous/Transcatheter Interventional Treatments of HF: Recommendations

See Table 32 for a summary of recommendations from this section.

Class I

1. **Coronary artery revascularization via CABG or percutaneous intervention is indicated for patients (HF*p*EF and HF*r*EF) on GDMT with angina and suitable coronary anatomy, especially for a left main stenosis (>50%) or left main equivalent disease.[10,12,14,848] *(Level of Evidence: C)***

Class IIa

1. **CABG to improve survival is reasonable in patients with mild to moderate LV systolic dysfunction (EF**

Table 31. Ten Most Common Co-Occurring Chronic Conditions Among Medicare Beneficiaries With HF (N=4 947 918), 2011

Beneficiaries Age ≥65 y (N=4 376 150)*			Beneficiaries Age <65 y (N=571 768)†		
	N	%		N	%
Hypertension	3 685 373	84.2	Hypertension	461 235	80.7
Ischemic heart disease	3 145 718	71.9	Ischemic heart disease	365 889	64.0
Hyperlipidemia	2 623 601	60.0	Diabetes	338 687	59.2
Anemia	2 200 674	50.3	Hyperlipidemia	325 498	56.9
Diabetes	2 027 875	46.3	Anemia	284 102	49.7
Arthritis	1 901 447	43.5	Chronic kidney disease	257 015	45.0
Chronic kidney disease	1 851 812	42.3	Depression	207 082	36.2
COPD	1 311 118	30.0	Arthritis	201 964	35.3
Atrial fibrillation	1 247 748	28.5	COPD	191 016	33.4
Alzheimer's disease/dementia	1 207 704	27.6	Asthma	88 816	15.5

*Mean No. of conditions is 6.1; median is 6.

†Mean No. of conditions is 5.5; median is 5.

COPD indicates chronic obstructive pulmonary disease; and HF, heart failure.

Data source: Centers for Medicare and Medicaid Services administrative claims data, January 2011–December 2011, from the Chronic Condition Warehouse (CCW), ccwdata.org.[847]

35% to 50%) and significant (≥70% diameter stenosis) multivessel CAD or proximal left anterior descending coronary artery stenosis when viable myocardium is present in the region of intended revascularization.[848–850] *(Level of Evidence: B)*

2. **CABG or medical therapy is reasonable to improve morbidity and cardiovascular mortality for patients with severe LV dysfunction (EF <35%), HF, and significant CAD.[309,851] *(Level of Evidence: B)***
3. **Surgical aortic valve replacement is reasonable for patients with critical aortic stenosis and a predicted surgical mortality of no greater than 10%.[852] *(Level of Evidence: B)***
4. **Transcatheter aortic valve replacement after careful candidate consideration is reasonable for patients with critical aortic stenosis who are deemed inoperable.[853] *(Level of Evidence: B)***

Class IIb

1. **CABG may be considered with the intent of improving survival in patients with ischemic heart disease with severe LV systolic dysfunction (EF <35%) and operable coronary anatomy whether or not viable myocardium is present.[307–309] *(Level of Evidence: B)***
2. **Transcatheter mitral valve repair or mitral valve surgery for functional mitral insufficiency is of uncertain benefit and should only be considered after careful candidate selection and with a background of GDMT.[854–857] *(Level of Evidence: B)***

Table 32. Recommendations for Surgical/Percutaneous/Transcatheter Interventional Treatments of HF

Recommendations	COR	LOE	References
CABG or percutaneous intervention is indicated for HF patients on GDMT with angina and suitable coronary anatomy, especially significant left main stenosis or left main equivalent	I	C	10, 12, 14, 848
CABG to improve survival is reasonable in patients with mild to moderate LV systolic dysfunction and significant multivessel CAD or proximal LAD stenosis when viable myocardium is present	IIa	B	848–850
CABG or medical therapy is reasonable to improve morbidity and mortality for patients with severe LV dysfunction (EF <35%), HF, and significant CAD	IIa	B	309, 851
Surgical aortic valve replacement is reasonable for patients with critical aortic stenosis and a predicted surgical mortality of no greater than 10%	IIa	B	852
Transcatheter aortic valve replacement is reasonable for patients with critical aortic stenosis who are deemed inoperable	IIa	B	853
CABG may be considered in patients with ischemic heart disease, severe LV systolic dysfunction, and operable coronary anatomy whether or not viable myocardium is present	IIb	B	307–309
Transcatheter mitral valve repair or mitral valve surgery for functional mitral insufficiency is of uncertain benefit	IIb	B	854–857
Surgical reverse remodeling or LV aneurysmectomy may be considered in HF*r*EF for specific indications, including intractable HF and ventricular arrhythmias	IIb	B	858

CABG indicates coronary artery bypass graft; CAD, coronary artery disease; COR, Class of Recommendation; EF, ejection fraction; GDMT, guideline-directed medical therapy; HF, heart failure; HF*r*EF, heart failure with reduced ejection fraction; LAD, left anterior descending; LOE, Level of Evidence; and LV, left ventricular.

3. **Surgical reverse remodeling or LV aneurysmectomy may be considered in carefully selected patients with HF*r*EF for specific indications, including intractable HF and ventricular arrhythmias.[858] *(Level of Evidence: B)***

Surgical therapies and percutaneous interventions that are commonly integrated, or at least considered, in HF management include coronary revascularization (eg, CABG, angioplasty, stenting); aortic valve replacement; mitral valve replacement or repair; septal myectomy or alcohol septal ablation for hypertrophic cardiomyopathy; surgical ablation of ventricular arrhythmia; MCS; and cardiac transplantation.[675,680,859,860] Surgical placement of ICDs or LV pacing leads is of historical importance but may be considered in situations where transvenous access is not feasible.

The most common reason for intervention is CAD. Myocardial viability indicates the likelihood of improved outcomes with either surgical or medical therapy but does not identify patients with greater survival benefit from revascularization.[304] The dictum of CABG for left main CAD and reduced LV function was considered absolute and subsequently extrapolated to all severities of LV dysfunction without a confirmatory evidence base.[848] Newer studies have addressed patients with multivessel CAD, HF, and at least moderately severe to severe LV systolic dysfunction.[861,862] Both surgical and medical therapies have similar outcomes, and decisions about revascularization should be made jointly by the HF team and cardiothoracic surgeon. The most important considerations in the decision to proceed with a surgical or interventional approach include coronary anatomy that is amenable to revascularization and appropriate concomitant GDMT. Valvular heart disease is not an infrequent cause of HF; however, when valvular disease is managed correctly and pre-emptively, its adverse consequences on ventricular mechanics can be ameliorated. The advent of effective transcatheter approaches to both mitral and aortic disease creates the need for greater considerations of structural interventions for patients with LV systolic dysfunction and valvular heart disease. To date, the surgical or transcatheter management of functional mitral insufficiency has not been proven superior to medical therapy. A decision to intervene in functional mitral regurgitation should be made on a case-by-case basis, and consideration should be given to participation in clinical trials and/or databases. The surgical or transcatheter management of critical aortic stenosis is an effective strategy with reasonable outcomes noted even in patients with advanced age (>80 years). Indications for other surgical or percutaneous interventions in the setting of HF are driven by other relevant guidelines or other sections of this guideline, including myomectomy for hypertrophic cardiomyopathy, surgical or electrophysiological procedures for AF, nondurable or durable MCS, and heart transplantation.

Several procedures under evaluation hold promise but are not yet appropriate for a guideline-driven indication (Table 33). This includes revascularization as a means to support cellular regenerative therapies. For patients willing to consider regenerative technologies, the ideal strategy is referral to an enrolling clinical trial at a center experienced in both high-risk revascularization and cell-based science.[863–865] Surgical reverse-ventricular remodeling (ventricular reconstruction) does not appear to be of benefit but may be considered in carefully selected patients with HF*r*EF for specified indications, including retractable HF and ventricular arrhythmias.[858]

Table 33. Surgical/Percutaneous/Transcatheter Interventions in Patients With HF

	References
Appropriate Guideline-Directed Surgical/Percutaneous/Transcatheter Interventions for HF	
1. Surgical or percutaneous revascularization	10, 12, 14
2. Surgical or transcatheter aortic valve replacement	852, 853
3. Surgical myomectomy or alcohol ablation for hypertrophic cardiomyopathy	11
4. Nondurable MCS for cardiogenic shock	668–671
5. Durable MCS for advanced HF	672–675
6. Heart transplantation	680
7. Surgical/electrophysiological ablation of ventricular tachycardia	866
Surgical/Percutaneous/Transcatheter Interventions Under Evaluation in Patients With HF	
1. Transcatheter intervention for functional mitral insufficiency	854–857
2. Left atrial resection/left atrial appendage removal, surgical or percutaneous, for AF	867
3. MCS for advanced HF as a bridge to recovery	868, 869

AF indicates atrial fibrillation; HF, heart failure; and MCS, mechanical circulatory support.

11. Coordinating Care for Patients With Chronic HF

11.1. Coordinating Care for Patients With Chronic HF: Recommendations

Class I

1. **Effective systems of care coordination with special attention to care transitions should be deployed for every patient with chronic HF that facilitate and ensure effective care that is designed to achieve GDMT and prevent hospitalization.[80,82,793,870–884] *(Level of Evidence: B)***
2. **Every patient with HF should have a clear, detailed, and evidence-based plan of care that ensures the achievement of GDMT goals, effective management of comorbid conditions, timely follow-up with the healthcare team, appropriate dietary and physical activities, and compliance with secondary prevention guidelines for cardiovascular disease. This plan of care should be updated regularly and made readily available to all members of each patient's healthcare team.[13] *(Level of Evidence: C)***
3. **Palliative and supportive care is effective for patients with symptomatic advanced HF to improve quality of life.[30,885–888] *(Level of Evidence: B)***

Education, support, and involvement of patients with HF and their families are critical and often complex, especially during transitions of care. Failure to understand and follow a detailed and often nuanced plan of care likely contributes to the high rates of HF 30-day rehospitalization and mortality seen across the United States.[61,889] One critical intervention to ensure effective care coordination and transition is the provision of a comprehensive plan of care, with easily understood,

culturally sensitive, and evidence-based educational materials, to patients with HF and/or caregivers during both hospital and office-based encounters. A comprehensive plan of care should promote successful patient self-care.[870,884,890] Hence, the plan of care for patients with HF should continuously address in detail a number of complex issues, including adherence to GDMT, timely follow-up with the healthcare professionals who manage the patient's HF and associated comorbidities, appropriate dietary and physical activities, including cardiac rehabilitation, and adherence to an extensive list of secondary prevention recommendations based on established guidelines for cardiovascular disease (Table 34). Clinicians must maintain vigilance about psychosocial, behavioral, and socioeconomic issues that patients with HF and their caregivers face, including access to care, risk of depression, and healthcare disparities.[639,891–895] For example, patients with HF who live in skilled nursing facilities are at higher risk for adverse events, with a 1-year mortality rate >50%.[896] Furthermore, community-dwelling patients with HF are often unable to afford the large number of medications prescribed, thereby leading to suboptimal medication adherence.[897]

11.2. Systems of Care to Promote Care Coordination for Patients With Chronic HF

Improved communication between clinicians and nurses, medication reconciliation, carefully planned transitions between care settings, and consistent documentation are examples of patient safety standards that should be ensured for all patients with HF. The National Quality Forum has also endorsed a set of patient-centered "Preferred Practices for Care Coordination,"[898] which detail comprehensive specifications for successful care coordination for patients and their families.

Systems of care designed to support patients with HF and other cardiac diseases can produce a significant improvement in outcomes. Furthermore, the Centers for Medicare and Medicaid Services is now financially penalizing hospitals for avoidable hospitalizations and readmissions, thereby emphasizing the importance of such systems-based care coordination of patients with HF.[899] However, the quality of evidence is mixed for specific components of HF clinical management interventions, such as home-based care,[871,872] disease management,[873,874,880] and remote telemonitoring programs.[80,875,876,878] Unfortunately, numerous and nonstandardized definitions of disease management,[873,879,880] including the specific elements that compose disease management, impede efforts to improve the care of patients with HF. Hence, more generic multidisciplinary strategies for improving the quality and cost-effectiveness of systems-based HF care should be evaluated with equal weight to those interventions focused on improving adherence to GDMT. For example, multidisciplinary approaches can reduce rates of hospitalization for HF. Programs involving specialized follow-up by a multidisciplinary team decrease all-cause hospitalizations and mortality; however, this has not been shown for "disease management programs" that focus only on self-care activities.[82,793,881,882,900] Furthermore, patient characteristics may be important predictors of HF and other cardiac disease–related survival and hospitalization. Overall, very few specific interventions have been consistently identified and successfully applied in clinical practice.[204,214,901–903]

See Online Data Supplements 42 and 43 for additional data on disease management and telemonitoring.

11.3. Palliative Care for Patients With HF

The core elements of comprehensive palliative care for HF delivered by clinicians include expert symptom assessment and management. Ongoing care should address symptom control, psychosocial distress, HRQOL, preferences about end-of-life care, caregiver support, and assurance of access to evidence-based disease-modifying interventions. The HF team can help patients and their families explore treatment options and prognosis. The HF and palliative care teams are best suited to help patients and families decide when end-of-life care (including hospice) is appropriate.[30,885–888,904] Assessment for frailty and dementia is part of this decision care process offered to the patient and family.

Data suggest that advance directives specifying limitations in end-of-life care are associated with significantly lower levels of Medicare spending, lower likelihood of in-hospital death, and higher use of hospice care in regions characterized by higher levels of end-of-life spending.[905] In newly diagnosed cancer patients, palliative care interventions delivered early have had a positive impact on survival and HRQOL. This approach may also be relevant for HF.[906] Access to formally trained palliative care specialists may be limited in ambulatory settings. Therefore, cardiologists, primary care physicians, physician assistants, advanced practice nurses, and other members of the HF healthcare team should be familiar with these local treatment options. Evaluation for cardiac transplantation or MCS in experienced centers should include formal palliative care consultation, which can improve advanced care planning and enhance the overall quality of decision making and integrated care for these patients, regardless of the advanced HF therapy selected.[907]

12. Quality Metrics/Performance Measures: Recommendations

Class I

1. **Performance measures based on professionally developed clinical practice guidelines should be used with the goal of improving quality of care for HF.[706,801,917] *(Level of Evidence: B)***

Class IIa

1. **Participation in quality improvement programs and patient registries based on nationally endorsed, clinical practice guideline–based quality and performance measures can be beneficial in improving the quality of HF care.[706,801] *(Level of Evidence: B)***

Quality measurement and accountability have become integral parts of medical practice over the past 2 decades. HF has been a specific target of quality measurement, improvement, and reporting because of its substantial impact on population morbidity and mortality. Commonly used performance measures for HF can be considered in 2 distinct categories: process measures and outcomes measures.

Process performance measures focus on the aspects of care that are delivered to a patient (eg, the prescription of a particular drug such as an ACE inhibitor in patients with LV systolic dysfunction and without contraindications). Process measures derive from the most definitive guideline recommendations (ie, class I and class III recommendations). A small group of process measures for hospitalized patients with HF have

Table 34. Plan of Care for Patients With Chronic HF

Plan of Care	Relevant Guideline Section/Reference
Guideline-directed medical and device therapy	
ACE inhibitor/ARB	Sections 7.3.2.2 and 7.3.2.3
Beta blocker	Section 7.3.2.4
Aldosterone receptor antagonist	Section 7.3.2.5
Diuretic	Sections 7.3.2.1 and 8.4
Hydralazine and isosorbide dinitrate	Section 7.3.2.6
Digoxin	Section 7.3.2.7
Discontinuation of drugs that may worsen HF	Section 7.3.2.9
Biomarker-related therapeutic goals	Section 6.3
HF-related devices (MCS, CRT, ICD)	Sections 7.3.4 and 7.4.5
Management of comorbidities (examples)	
Ischemic heart disease	2012 ACCF/AHA SIHD Guideline[14]
Antithrombotic therapies	Section 7.3.2.8.1
Arrhythmia/arrhythmia risk	Sections 7.3.2.9.2 and 9.1
Hypertension	Section 7.1.1, JNC-VII[27]
Diabetes mellitus	2012 ADA Standards[90]
Chronic renal failure	Section 8.5
Chronic obstructive pulmonary disease	2011 ACCP/ATS/ERS Guideline[908]
Secondary prevention interventions (eg, lipids, smoking cessation, influenza and pneumococcal vaccines)	2011 AHA/ACCF Secondary Prevention and Risk Reduction Guidelines and Centers for Disease Control Adult Vaccinations[13,909,910]
Patient/family education	
Diet and fluid restriction, weight monitoring	Sections 7.3.1.1, 7.3.1.3, 7.3.1.5, and 7.4.3
Recognizing signs and symptoms of worsening HF	Table 24
Risk assessment and prognosis	Sections 3, 4.6, 6.1.2
QOL assessment	2012 AHA Scientific Statement on Advanced HF[30]
Advance care planning (eg, palliative care and advance directives)	Section 11.3[30,888]
CPR training for family members	AHA Family & Friends CPR[911]
Social support	Section 7.3.1.2
Physical activity/cardiac rehabilitation	
Exercise regimen	Sections 7.3.1.5 and 7.3.1.6
Activities of daily living	Section 7.3.1.6
Functional status assessment and classification	Section 3
Psychosocial factors	
Sex-specific issues	2011 AHA Guidelines for the Prevention of Cardiovascular Disease in Women[912]
Sexual activity	2012 AHA Scientific Statement on Sexual Activity[913]
Depression screening	US Preventive Services Task Force Guidelines[914]
Clinician follow-up and care coordination	
Cardiologists and other relevant specialists	2000 AHA Scientific Statement for Team Management of Patients With HF[900]
Primary care physician	NQF Preferred Practices for Care Coordination[898]
Advanced practice nurse	Section 11.1–11.3, Joint Commission 2013 National Patient Safety Goals[915]
Other healthcare providers (eg, home care)	
Medication reconciliation Establishment of electronic personal health records	HHS Meaningful Use Criteria
Socioeconomic and cultural factors	
Culturally sensitive issues	NQF: A Comprehensive Framework and Preferred Practices for Measuring and Reporting Cultural Competency[916]
Education and health literacy	Section 7.3.1.1
Social support	Section 7.3.1.2

ACCF indicates American College of Cardiology Foundation; ACCP, American College of Chest Physicians; ACE, angiotensin-converting enzyme; ADA, American Diabetes Association; AHA, American Heart Association; ARB, angiotensin-receptor blocker; ATS, American Thoracic Society; CPR, cardiopulmonary resuscitation; CRT, cardiac resynchronization therapy; ERS, European Respiratory Society; HF, heart failure; HHS, Health and Human Services; ICD, implantable cardioverter-defibrillator; JNC, Joint National Committee; MCS, mechanical circulatory support; NQF, National Quality Forum; QOL, quality of life; and SIHD, stable ischemic heart disease.

Table 35. Outcome Measures for HF

Measure	Developer
Congestive HF mortality rate (NQF endorsed)	Agency for Health Research and Quality
HF 30-day mortality rate (NQF endorsed)	Centers for Medicare and Medicaid Services
Congestive HF admission rate (NQF endorsed)	Agency for Health Research and Quality
HF 30-day risk-standardized HF readmission rate (NQF endorsed)	Centers for Medicare and Medicaid Services

HF indicates heart failure; and NQF, National Quality Forum.

been reported to the public by the Centers for Medicare and Medicaid Services as part of the Hospital Compare program.[918]

Measures used to characterize the care of patients with HF should be those developed in a multiorganizational consensus process using an explicit methodology focusing on measurability, validity, reliability, feasibility, and ideally, correlation with patient outcomes,[919,920] and with transparent disclosure and management of possible conflicts of interest. In the case of HF, several national outcome measures are currently in use (Table 35), and the ACCF/AHA/American Medical Association–Physician Consortium for Performance Improvement recently published revised performance measures document includes several process measures for both inpatient and outpatient HF care (Table 36).[921] Of note, the ACCF/AHA distinguish between processes of care that can be considered "Performance Measures" (ie, suitable for use for accountability purposes) and "Quality Metrics" (ie, suitable for use for quality improvement but not accountability).[922]

Measures are appealing for several reasons; by definition, they reflect the strongest guideline recommendations. When appropriately specified, they are relatively easy to calculate and

Table 36. ACCF/AHA/AMA-PCPI 2011 HF Measurement Set

Measure	Description*	Care Setting	Level of Measurement
1. LVEF assessment	Percentage of patients aged ≥18 y with a diagnosis of HF for whom the quantitative or qualitative results of a recent or prior (any time in the past) LVEF assessment is documented within a 12-mo period	Outpatient	Individual practitioner
2. LVEF assessment	Percentage of patients aged ≥18 y with a principal discharge diagnosis of HF with documentation in the hospital record of the results of an LVEF assessment performed either before arrival or during hospitalization, OR documentation in the hospital record that LVEF assessment is planned for after discharge	Inpatient	• Individual practitioner • Facility
3. Symptom and activity assessment	Percentage of patient visits for those patients aged ≥18 y with a diagnosis of HF with quantitative results of an evaluation of both current level of activity and clinical symptoms documented	Outpatient	Individual practitioner
4. Symptom management†	Percentage of patient visits for those patients aged ≥18 y with a diagnosis of HF and with quantitative results of an evaluation of both level of activity AND clinical symptoms documented in which patient symptoms have improved or remained consistent with treatment goals since last assessment OR patient symptoms have demonstrated clinically important deterioration since last assessment with a documented plan of care	Outpatient	Individual practitioner
5. Patient self-care education†‡	Percentage of patients aged ≥18 y with a diagnosis of HF who were provided with self-care education on ≥3 elements of education during ≥1 visits within a 12-mo period	Outpatient	Individual practitioner
6. Beta-blocker therapy for LVSD (outpatient and inpatient setting)	Percentage of patients aged ≥18 y with a diagnosis of HF with a current or prior LVEF <40% who were prescribed beta-blocker therapy with bisoprolol, carvedilol, or sustained-release metoprolol succinate either within a 12-mo period when seen in the outpatient setting or at hospital discharge	Inpatient and outpatient	• Individual practitioner • Facility
7. ACE inhibitor or ARB therapy for LVSD (outpatient and inpatient setting)	Percentage of patients aged ≥18 y with a diagnosis of HF with a current or prior LVEF <40% who were prescribed ACE inhibitor or ARB therapy either within a 12-mo period when seen in the outpatient setting or at hospital discharge	Inpatient and outpatient	• Individual practitioner • Facility
8. Counseling about ICD implantation for patients with LVSD on combination medical therapy†‡	Percentage of patients aged ≥18 y with a diagnosis of HF with current LVEF ≤35% despite ACE inhibitor/ARB and beta-blocker therapy for at least 3 mo who were counseled about ICD implantation as a treatment option for the prophylaxis of sudden death	Outpatient	Individual practitioner
9. Postdischarge appointment for HF patients	Percentage of patients, regardless of age, discharged from an inpatient facility to ambulatory care or home health care with a principal discharge diagnosis of HF for whom a follow-up appointment was scheduled and documented, including location, date, and time for a follow-up office visit or home health visit (as specified)	Inpatient	Facility

NB, Regarding test measure no. 8, implantation of ICD must be consistent with published guidelines. This measure is intended to promote counseling only.

*Refer to the complete measures for comprehensive information, including measure exception.

†Test measure designated for use in internal quality improvement programs only. These measures are not appropriate for any other purpose (eg, pay for performance, physician ranking, or public reporting programs).

‡New measure.

ACCF indicates American College of Cardiology Foundation; ACE, angiotensin-converting enzyme; AHA, American Heart Association; AMA-PCPI, American Medical Association–Physician Consortium for Performance Improvement; ARB, angiotensin-receptor blocker; HF, heart failure; ICD, implantable cardioverter-defibrillator; LVEF, left ventricular ejection fraction; and LVSD, left ventricular systolic dysfunction.

Adapted from Bonow et al.[921]

they provide a clear target for improvement. However, they do not capture the broader range of care; they apply only to those patients without contraindications to therapy. Evidence of the relation between better performance with respect to process measures and patient outcomes is conflicting, and performance rates for those measures that have been used as part of public reporting programs are generally high for all institutions, limiting the ability of these measures to identify high- and low-performing centers.

These limitations of process measures have generated interest in the use of outcomes measures as a complementary approach to characterize quality. With respect to HF, 30-day mortality and 30-day readmission are reported by the Centers for Medicare and Medicaid Services as part of the Hospital Compare program (Table 35) and are incorporated in the Centers for Medicare and Medicaid Services value-based purchasing program.[918] Outcomes measures are appealing because they apply universally to almost all patients, and they provide a perspective on the performance of health systems.[923] On the other hand, they are limited by the questionable adequacy of risk adjustment and by the challenges of improvement. The ACCF and AHA have published criteria that characterize the necessary attributes of robust outcomes measures.[924]

See Online Data Supplement 44 for additional data on quality metrics and performance measures.

13. Evidence Gaps and Future Research Directions

Despite the objective evidence compiled by the writing committee on the basis of hundreds of clinical trials, there are huge gaps in our knowledge base about many fundamental aspects of HF care. Some key examples include an effective management strategy for patients with HF*p*EF beyond blood pressure control; a convincing method to use biomarkers in the optimization of medical therapy; the recognition and treatment of cardiorenal syndrome; and the critical need for improving patient adherence to therapeutic regimens. Even the widely embraced dictum of sodium restriction in HF is not well supported by current evidence. Moreover, the majority of the clinical trials that inform GDMT were designed around the primary endpoint of mortality, so that there is less certainty about the impact of therapies on the HRQOL of patients. It is also of major concern that the majority of RCTs failed to randomize a sufficient number of the elderly, women, and underrepresented minorities, thus, limiting insight into these important patient cohorts. A growing body of studies on patient-centered outcomes research is likely to address some of these deficiencies, but time will be required.

HF is a syndrome with a high prevalence of comorbidities and multiple chronic conditions, but most guidelines are developed for patients with a single disease. Nevertheless, the coexistence of additional diseases such as arthritis, renal insufficiency, diabetes mellitus, or chronic lung disease with the HF syndrome should logically require a modification of treatment, outcome assessment, or follow-up care. About 25% of Americans have multiple chronic conditions; this figure rises to 75% in those >65 years of age, including the diseases referred to above, as well as asthma, hypertension, cognitive disorders, or depression.[847] Most RCTs in HF specifically excluded patients with significant other comorbidities from enrollment, thus limiting our ability to generalize our recommendations to many real-world patients. Therefore, the clinician must, as always, practice the art of using the best of the guideline recommendations as they apply to a specific patient.

Future research will need to focus on novel pharmacological therapies, especially for hospitalized HF; regenerative cell-based therapies to restore myocardium; and new device platforms that will either improve existing technologies (eg, CRT, ICD, left VAD) or introduce simpler, less morbid devices that are capable of changing the natural history of HF. What is critically needed is an evidence base that clearly identifies best processes of care, especially in the transition from hospital to home. Finally, preventing the burden of this disease through more successful risk modification, sophisticated screening, perhaps using specific omics technologies (ie, systems biology) or effective treatment interventions that reduce the progression from stage A to stage B is an urgent need.

Presidents and Staff

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KEY WORDS: AHA Scientific Statements ■ cardio-renal physiology/pathophysiology ■ congestive heart failure ■ CV surgery: transplantation, ventricular assistance, cardiomyopathy ■ epidemiology ■ health policy and outcome research ■ heart failure ■ other heart failure

Appendix 1. Author Relationships With Industry and Other Entities (Relevant)—2013 ACCF/AHA Guideline for the Management of Heart Failure

Committee Member	Employment	Consultant	Speaker's Bureau	Ownership/ Partnership/ Principal	Personal Research	Institutional, Organizational, or Other Financial Benefit	Expert Witness	Voting Recusals by Section*
Clyde W. Yancy, *Chair*	Northwestern University—Chief, Division of Cardiology and Magerstadt Professor of Medicine	None	None	None	None	None	None	None
Mariell Jessup, *Vice Chair*	University of Pennsylvania—Professor of Medicine	None	None	None	• Amgen • Celladon • HeartWare	None	None	7.4.4 7.4.5 7.4.6 10
Biykem Bozkurt	Michael E. DeBakey VA Medical Center—The Mary and Gordon Cain Chair and Professor of Medicine	None	None	None	None	None	None	None
Javed Butler	Emory Healthcare—Director of Heart Failure Research; Emory University School of Medicine—Professor of Medicine	• Amgen • CardioMEMS • Gambro • Takeda	None	None	None	• Amgen • Biotronic • Boston Scientific • CardioMEMS • Corthera† • FoldRx • iOcopsys • Johnson & Johnson • Medtronic • Thoratec • World Heart	None	6.4 7.1 7.2 7.3.2 7.3.3 7.3.4 7.4.4 7.4.5 7.4.6 8.6 8.7 10
Donald E. Casey, Jr	Clinically Integrated Physician Network, NYU Langone Medical Center—Vice President and Medical Director	None	None	None	None	None	None	None
Mark H. Drazner	University of Texas Southwestern Medical Center—Professor, Internal Medicine	None	None	None	• HeartWare • Scios/Johnson & Johnson†	• Medtronic • Thoratec†	None	7.1 7.2 7.3.2 7.3.4 7.4.4 7.4.5 7.4.6 8.6 8.7 10
Gregg C. Fonarow	Director Ahmanson—UCLA Cardiomyopathy Center; Co-Chief—UCLA Division of Cardiology	• Gambro (formerly CHF Solutions) • Medtronic • Novartis† • Takeda	None	None	• Gambro (formerly CHF Solutions) • Novartis†	• Medtronic	None	7.1 7.2 (Class IIa) 7.3.2 7.3.4 8.3 8.4 8.7 10
Stephen A. Geraci	Quillen College of Medicine/East Tennessee State University—Chairman of Internal Medicine	None	None	None	None	None	None	None

(*continued*)

Appendix 1. Continued

Committee Member	Employment	Consultant	Speaker's Bureau	Ownership/ Partnership/ Principal	Personal Research	Institutional, Organizational, or Other Financial Benefit	Expert Witness	Voting Recusals by Section*
Tamara Horwich	Ahmanson—UCLA Cardiomyopathy Center—Assistant Professor of Medicine, Cardiology	None	None	None	None	None	None	None
James L. Januzzi	Harvard Medical School—Associate Professor of Medicine; Massachusetts General Hospital—Director, Cardiac Intensive Care Unit	• Critical Diagnostics† • Roche Diagnostics†	None	None	• Critical Diagnostics† • Roche Diagnostics†	None	None	6.2 6.3
Maryl R. Johnson	University of Wisconsin, Madison—Professor of Medicine, Director Heart Failure and Transplantation	None	None	None	None	None	None	None
Edward K. Kasper	Johns Hopkins Hospital— E. Cowles Andrus Professor in Cardiology Director, Clinical Cardiology	None	None	None	None	None	None	None
Wayne C. Levy	University of Washington—Professor of Medicine, Division of Cardiology	• Cardiac Dimensions† • CardioMEMS • GE/Scios/ Johnson & Johnson	• Amarin • Boehringer Ingelheim • GlaxoSmithKline	None	• Amgen† • HeartWare†	• Amgen • Epocrates • GE Healthcare • HeartWare • Thoratec	None	6.4 6.5 7.1 7.2 7.3.1 7.3.2 7.3.4 7.4.5 8.3 8.6 8.7 10
Frederick A. Masoudi	University of Colorado, Denver—Associate Professor of Medicine, Division of Cardiology	None	None	None	None	None	None	None
Patrick E. McBride	University of Wisconsin School of Medicine and Public Health—Professor of Medicine and Family Medicine, Associate Dean for Students, Associate Director, Preventive Cardiology	None	None	None	None	None	None	None
John J.V. McMurray	University of Glasgow, Scotland, BHF Glasgow Cardiovascular Research Center—Professor of Medical Cardiology	None	None	None	• GlaxoSmithKline† • Novartis • Roche (DSMB)	• Novartis (PARADIGM–PI)	None	6.2 6.3 7.1 7.2 (Class I and Class III) 7.3.2 8.3 8.7

(*continued*)

Appendix 1. Continued

Committee Member	Employment	Consultant	Speaker's Bureau	Ownership/ Partnership/ Principal	Personal Research	Institutional, Organizational, or Other Financial Benefit	Expert Witness	Voting Recusals by Section*
Judith E. Mitchell	SUNY Downstate Medical Center—Director, Heart Failure Center; Associate Professor of Medicine	None	None	None	None	None	None	None
Pamela N. Peterson	University of Colorado, Denver Health Medical Center—Associate Professor of Medicine, Division of Cardiology	None	None	None	None	None	None	None
Barbara Riegel	University of Pennsylvania School of Nursing—Professor	None	None	None	None	None	None	None
Flora Sam	Boston University School of Medicine, Whitaker Cardiovascular Institute—Associate Professor of Medicine, Division of Cardiology/ Cardiomyopathy Program	None	None	None	None	None	None	None
Lynne W. Stevenson	Brigham and Women's Hospital Cardiovascular Division—Director, Cardiomyopathy and Heart Failure Program	None	None	None	• Biosense Webster	None	None	7.3.4
W.H. Wilson Tang	Cleveland Clinic Foundation—Associate Professor of Medicine, Research Director for Heart Failure/Transplant	• Medtronic • St. Jude Medical	None	None	• Abbott† • FoldRx • Johnson & Johnson • Medtronic† • St. Jude Medical†	None	None	6.2 6.3 7.1 7.2 7.3.2 7.3.3 7.3.4 8.6 8.7 10
Emily J. Tsai	Temple University School of Medicine—Assistant Professor of Medicine, Cardiology	None	None	None	None	None	None	None
Bruce L. Wilkoff	Cleveland Clinic—Director, Cardiac Pacing and Tachyarrhythmia Devices; Director, Clinical EP Research	None	None	None	• Biotronic • Boston Scientific • Medtronic • St. Jude Medical	None	None	7.2 (Class IIa) 7.3.4 10

This table represents the relationships of committee members with industry and other entities that were determined to be relevant to this document. These relationships were reviewed and updated in conjunction with all meetings and/or conference calls of the writing committee during the document development process. The table does not necessarily reflect relationships with industry at the time of publication. A person is deemed to have a significant interest in a business if the interest represents ownership of ≥5% of the voting stock or share of the business entity, or ownership of ≥$10 000 of the fair market value of the business entity; or if funds received by the person from the business entity exceed 5% of the person's gross income for the previous year. Relationships that exist with no financial benefit are also included for the purpose of transparency. Relationships in this table are modest unless otherwise noted.

According to the ACCF/AHA, a person has a *relevant* relationship IF: a) The *relationship or interest* relates to the same or similar subject matter, intellectual property or asset, topic, or issue addressed in the *document*; or b) The *company/entity* (with whom the relationship exists) makes a drug, drug class, or device addressed in the *document*, or makes a competing drug or device addressed in the *document*; or c) The *person or a member of the person's household*, has a reasonable potential for financial, professional or other personal gain or loss as a result of the issues/content addressed in the *document*.

*Writing committee members are required to recuse themselves from voting on sections to which their specific relationships with industry and other entities may apply. Section numbers pertain to those in the full-text guideline.

†Indicates significant relationship.

DSMB indicates Data Safety Monitoring Board; EP, electrophysiology; NYU, New York University; PARADIGM, a Multicenter, Randomized, Double-blind, Parallel Group, Active-controlled Study to Evaluate the Efficacy and Safety of LCZ696 Compared to Enalapril on Morbidity and Mortality in Patients With Chronic Heart Failure and Reduced Ejection Fraction; PI, Principal Investigator; SUNY, State University of New York; UCLA, University of California, Los Angeles; and VA, Veterans Affairs.

Appendix 2. Reviewer Relationships With Industry and Other Entities (Relevant)—2013 ACCF/AHA Guideline for the Management of Heart Failure

Reviewer	Representation	Employment	Consultant	Speaker's Bureau	Ownership/ Partnership/ Principal	Personal Research	Institutional, Organizational, or Other Financial Benefit	Expert Witness
Nancy Albert	Official Reviewer—ACCF/AHA Task Force on Practice Guidelines	Kaufman Center for Heart Failure—Senior Director of Nursing Research	• BG Medicine • Medtronic • Merck†	None	None	None	None	None
Kathleen Grady	Official Reviewer—AHA	Bluhm Cardiovascular Institute—Administrative Director, Center for Heart Failure	None	None	None	None	None	None
Paul Hauptman	Official Reviewer—AHA	St Louis University School of Medicine—Professor of Internal Medicine, Division of Cardiology	• BG Medicine • BioControl Medical • Otsuka*	None	None	None	• EvaHeart†	None
Hector Ventura	Official Reviewer—ACCF Board of Governors	Ochsner Clinic Foundation—Director, Section of Cardiomyopathy and Heart Transplantation	• Otsuka	• Actelion	None	None	None	None
Mary Norine Walsh	Official Reviewer—ACCF Board of Trustees	St. Vincent Heart Center of Indiana—Medical Director	• United Healthcare	None	None	None	None	None
Jun Chiong	Organizational Reviewer—ACCP	Loma Linda University—Associate Clinical Professor of Medicine	None	None	None	None	• Otsuka (DSMB)	None
David DeLurgio	Organizational Reviewer—HRS	The Emory Clinic—Associate Professor, Director of EP Laboratory	None	None	None	None	None	None
Folashade Omole	Organizational Reviewer—AAFP	Morehouse School of Medicine—Associate Professor of Clinical Family Medicine	None	None	None	None	None	None
Robert Rich, Jr	Organizational Reviewer—AAFP	Bladen Medical Associates—Family Practice	None	None	None	None	None	None
David Taylor	Organizational Reviewer—ISHLT	Cleveland Clinic, Department of Cardiology—Professor of Medicine	None	None	None	None	• Biotronix† • Genentech† • HeartWare† • ISHLT • Novartis† • St. Jude's Medical†	None
Kimberly Birtcher	Content Reviewer—ACCF Cardiovascular Team Council	University of Houston College of Pharmacy—Clinical Professor	None	None	None	None	None	None
Kay Blum	Content Reviewer—ACCF Cardiovascular Team Council	Medstar Southern Maryland Hospital Center—Nurse Practitioner	None	None	None	None	None	None

(*continued*)

Appendix 2. Continued

Reviewer	Representation	Employment	Consultant	Speaker's Bureau	Ownership/ Partnership/ Principal	Personal Research	Institutional, Organizational, or Other Financial Benefit	Expert Witness
Michael Chan	Content Reviewer—ACCF Cardiovascular Team Council	Royal Alexandra Hospital—Co-Director, Heart Function Program; University of Alberta—Associate Clinical Professor of Medicine	None	None	None	None	• Medtronic	None
Jane Chen	Content Reviewer—ACCF EP Committee	Washington University School of Medicine—Assistant Professor of Medicine	• Medtronic • St. Jude Medical	None	None	None	None	None
Michael Clark	Content Reviewer—ACCF Cardiovascular Team Council	North Texas Cardiology and EP—Associate Professor	None	• Abbott Pharma	None	None	None	None
Marco Costa	Content Reviewer—ACCF Imaging Council	University Hospital for Cleveland—Professor of Medicine	• Abbott Vascular • Boston Scientific • Cardiokinetix* • Medtronic • St. Jude Medical	• Daiichi-Sankyo • Eli Lilly • Sanofi	None	None	• Abbott Vascular* • Boston Scientific • Cardiokinetix† • Medtronic* • St. Jude Medical	None
Anita Deswal	Content Reviewer	Baylor College of Medicine—Associate Professor of Medicine	None	None	None	• Amgen† • Novartis†	None	None
Steven Dunn	Content Reviewer—ACCF Prevention Committee	University of Virginia Health System—Clinical Pharmacy Specialist	None	None	None	None	None	None
Andrew Epstein	Content Reviewer	University of Pennsylvania—Professor of Medicine	• Biotronic • Boehringer Ingelheim • Medtronic • Zoll	None	None	• Biosense Webster* • Boston Scientific* • Cameron Health*	• Boston Scientific* • St. Jude Medical*	None
Justin Ezekowitz	Content Reviewer—AHA	Mazankowski Alberta Heart Institute—Director, Heart Function Clinic	• Abbott Labs • AstraZeneca • Pfizer	None	None	• Amgen • Bristol-Myers Squibb	None	None
Gerasimos Filippatos	Content Reviewer	University of Athens—Department of Cardiology	None	None	None	None	• Corthera • Vifor	None
Linda Gillam	Content Reviewer—ACCF Imaging Council	Morristown Medical Center—Professor of Cardiology	None	None	None	None	• Edwards Lifesciences†	None
Paul Heidenreich	Content Reviewer	Stanford VA Palo Alto Medical Center—Assistant Professor of Medicine	None	None	None	• Medtronic†	None	None
Paul Hess	Content Reviewer—ACCF EP Committee	Duke University School of Medicine—Fellow	None	None	None	None	None	None

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Appendix 2. Continued

Reviewer	Representation	Employment	Consultant	Speaker's Bureau	Ownership/ Partnership/ Principal	Personal Research	Institutional, Organizational, or Other Financial Benefit	Expert Witness
Sharon Ann Hunt	Content Reviewer	Stanford University Medical Center—Professor, Department of Cardiovascular Medicine	None	None	None	None	None	None
Charles McKay	Content Reviewer—ACCF Council on Cardiovascular Care for Older Adults	Harbor-UCLA Medical Center—Professor of Medicine	None	None	None	None	None	None
James McClurken	Content Reviewer—ACCF Surgeons' Scientific Council	Temple University School of Medicine—Director of Cardiothoracic Perioperative Services	None	None	None	None	None	None
Wayne Miller	Content Reviewer—ACCF Heart Failure and Transplant Council	Mayo Clinic—Professor of Medicine	None	None	None	None	None	None
Rick Nishimura	Content Reviewer	Mayo Clinic—Professor of Medicine	None	None	None	None	None	None
Donna Petruccelli	Content Reviewer—ACCF Heart Failure and Transplant Council	Lehigh Valley Health Network—Heart Failure Nurse Practitioner/ Clinical Nurse Specialist, Center for Advanced Heart Failure	None	None	None	None	None	None
Geetha Raghuveer	Content Reviewer—ACCF Board of Governors	Children's Mercy Hospital—Associate Professor of Pediatrics	None	None	None	None	None	None
Pasala Ravichandran	Content Reviewer—ACCF Surgeons' Scientific Council	Oregon Health & Science University—Associate Professor	None	None	None	None	None	None
Michael Rich	Content Reviewer—ACCF Council on Cardiovascular Care for Older Adults	Washington University School of Medicine—Professor of Medicine	None	None	None	None	None	None
Anitra Romfh	Content Reviewer—ACCF Adult Congenital and Pediatric Cardiology Council	Children's Hospital Boston—Clinical Fellow in Pediatrics	None	None	None	None	None	None

(*continued*)

Appendix 2. Continued

Reviewer	Representation	Employment	Consultant	Speaker's Bureau	Ownership/ Partnership/ Principal	Personal Research	Institutional, Organizational, or Other Financial Benefit	Expert Witness
Andrea Russo	Content Reviewer—ACCF Task Force on Appropriate Use Criteria	Cooper University Hospital—Professor of Medicine	• Biotronik • Boston Scientific • Cameron Health • Medtronic • St. Jude Medical	None	None	• Cameron Health • Medtronic	None	None
Dipan Shah	Content Reviewer—ACCF Imaging Council	Methodist DeBakey Heart Center—Director	None	• AstraZeneca* • Lantheus Medical Imaging	None	None	• Astellas Pharma • Siemens Medical Solutions*	None
Randy Starling	Content Reviewer	Cleveland Clinic, Department of Cardiovascular Medicine—Vice Chairman	• Novartis	None	None	None	• Biotronik • Medtronic	None
Karen Stout	Content Reviewer—ACCF Adult Congenital and Pediatric Cardiology Council	University of Washington—Director, Adult Congenital Heart Disease Program	None	None	None	None	None	None
John Teerlink	Content Reviewer	San Francisco VA Medical Center—Professor of Medicine	• Amgen* • Anexon • CardioMEMS* • Cytokinetics • Novartis* • St. Jude Medical* • Scios/Johnson & Johnson • Trevena	None	None	None	• Amgen* • Merck • Novartis*	None
Robert Touchon	Content Reviewer—ACCF Prevention Committee	Marshall University, Joan C. Edwards School of Medicine—Professor of Medicine	None	None	None	None	None	None
Hiroyuki Tsutsui	Content Reviewer	Hokkaido University—Professor of Medicine	• Daiichi-Sankyo* • Novartis* • Pfizer • Takeda*	None	None	None	None	None
Robert Vincent	Content Reviewer—ACCF Adult Congenital and Pediatric Cardiology Council	Emory University School of Medicine—Professor of Pediatrics	None	None	None	None	• AGA	None

This table represents the relationships of reviewers with industry and other entities that were disclosed at the time of peer review and determined to be relevant to this document. It does not necessarily reflect relationships with industry at the time of publication. A person is deemed to have a significant interest in a business if the interest represents ownership of ≥5% of the voting stock or share of the business entity, or ownership of ≥$10 000 of the fair market value of the business entity; or if funds received by the person from the business entity exceed 5% of the person's gross income for the previous year. A relationship is considered to be modest if it is less than significant under the preceding definition. Relationships that exist with no financial benefit are also included for the purpose of transparency. Relationships in this table are modest unless otherwise noted. Names are listed in alphabetical order within each category of review.

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*Significant relationship.

†No financial benefit.

AAFP indicates American Academy of Family Physicians; ACCF, American College of Cardiology Foundation; ACCP, American College of Chest Physicians; AHA, American Heart Association; DSMB, data safety monitoring board; EP, electrophysiology; HRS, Heart Rhythm Society; ISHLT, International Society for Heart and Lung Transplantation; and VA, Veterans Affairs.

Appendix 3. Abbreviations

ACE = angiotensin-converting enzyme
ACS = acute coronary syndrome
AF = atrial fibrillation
ARB = angiotensin-receptor blocker
BMI = body mass index
BNP = B-type natriuretic peptide
CABG = coronary artery bypass graft
CAD = coronary artery disease
CRT = cardiac resynchronization therapy
DCM = dilated cardiomyopathy
ECG = electrocardiogram
EF = ejection fraction
GDMT = guideline-directed medical therapy
HbA1c = hemoglobin A1c
HF = heart failure
HF*p*EF = heart failure with preserved ejection fraction
HF*r*EF = heart failure with reduced ejection fraction
HRQOL = health-related quality of life
ICD = implantable cardioverter-defibrillator
LBBB = left bundle-branch block
LV = left ventricular
LVEF = left ventricular ejection fraction
MCS = mechanical circulatory support
MI = myocardial infarction
NSAIDs = nonsteroidal anti-inflammatory drugs
NT-proBNP = N-terminal pro-B-type natriuretic peptide
NYHA = New York Heart Association
PUFA = polyunsaturated fatty acids
RCT = randomized controlled trial
SCD = sudden cardiac death
VAD = ventricular assist device