

CLINICAL PRACTICE GUIDELINE: FOCUSED UPDATE

2017 ACC/AHA/HFSA Focused Update of the 2013 ACCF/AHA Guideline for the Management of Heart Failure



A Report of the American College of Cardiology/American Heart Association
Task Force on Clinical Practice Guidelines and the Heart Failure Society of America

*Developed in Collaboration with the American Academy of Family Physicians,
American College of Chest Physicians, and International Society for Heart and Lung Transplantation*

Writing Group Members*

Clyde W. Yancy, MD, MSc, MACC, FAHA, FHFSA, *Chair*
Mariell Jessup, MD, FACC, FAHA, *Vice Chair*

Biykem Bozkurt, MD, PhD, FACC, FAHA*†
Javed Butler, MD, MBA, MPH, FACC, FAHA*‡
Donald E. Casey, Jr, MD, MPH, MBA, FACC§
Monica M. Colvin, MD, FAHA||
Mark H. Drazner, MD, MSc, FACC, FAHA, FHFSA‡
Gerasimos S. Filippatos, MD*
Gregg C. Fonarow, MD, FACC, FAHA, FHFSA*‡
Michael M. Givertz, MD, FACC, FHFSA*¶
Steven M. Hollenberg, MD, FACC#
JoAnn Lindenfeld, MD, FACC, FAHA, FHFSA*¶

Frederick A. Masoudi, MD, MSPH, FACC**
Patrick E. McBride, MD, MPH, FACC††
Pamela N. Peterson, MD, FACC, FAHA‡
Lynne Warner Stevenson, MD, FACC*‡
Cheryl Westlake, PhD, RN, ACNS-BC, FAHA, FHFSA¶

*Writing group members are required to recuse themselves from voting on sections to which their specific relationships with industry may apply; see [Appendix 1](#) for detailed information. †ACC/AHA Task Force on Clinical Practice Guidelines Liaison. ‡ACC/AHA Representative. §ACP Representative. ||ISHLT Representative. ¶HFSA Representative. #CHEST Representative. **ACC/AHA Task Force on Performance Measures Representative. ††AAFP Representative.

This document was approved by the American College of Cardiology Clinical Policy Approval Committee, the American Heart Association Science Advisory and Coordinating Committee, the American Heart Association Executive Committee, and the Heart Failure Society of America Executive Committee in April 2017.

The American College of Cardiology requests that this document be cited as follows: Yancy CW, Jessup M, Bozkurt B, Butler J, Casey DE Jr, Colvin MM, Drazner MH, Filippatos GS, Fonarow GC, Givertz MM, Hollenberg SM, Lindenfeld J, Masoudi FA, McBride PE, Peterson PN, Stevenson LW, Westlake C. 2017 ACC/AHA/HFSA focused update of the 2013 ACCF/AHA guideline for the management of heart failure: a report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines and the Heart Failure Society of America. *J Am Coll Cardiol*. 2017;70:776-803.

This article has been copublished in *Circulation* and the *Journal of Cardiac Failure*.

Copies: This document is available on the World Wide Web sites of the American College of Cardiology (www.acc.org), the American Heart Association (professional.heart.org), and the Heart Failure Society of America (www.hfsa.org). For copies of this document, please contact the Elsevier Reprint Department via fax (212-633-3820) or e-mail (reprints@elsevier.com).

Permissions: Multiple copies, modification, alteration, enhancement, and/or distribution of this document are not permitted without the express permission of the American College of Cardiology. Requests may be completed online via the Elsevier site (<https://www.elsevier.com/about/our-business/policies/copyright/permissions>).

ACC/AHA Task Force Members

Glenn N. Levine, MD, FACC, FAHA, *Chair*
Patrick T. O’Gara, MD, FACC, FAHA, *Chair-Elect*
Jonathan L. Halperin, MD, FACC, FAHA,
Immediate Past Chair††

Sana M. Al-Khatib, MD, MHS, FACC, FAHA
Kim K. Birtcher, PHARM D, MS, AACC
Biykem Bozkurt, MD, PhD, FACC, FAHA
Ralph G. Brindis, MD, MPH, MACC††
Joaquin E. Cigarroa, MD, FACC
Lesley H. Curtis, PhD, FAHA
Lee A. Fleisher, MD, FACC, FAHA

Federico Gentile, MD, FACC
Samuel Gidding, MD, FAHA
Mark A. Hlatky, MD, FACC
John Ikonomidis, MD, PhD, FAHA
José Joglar, MD, FACC, FAHA
Susan J. Pressler, PhD, RN, FAHA
Duminda N. Wijesundera, MD, PhD

††Former Task Force member; current member during the writing effort.

TABLE OF CONTENTS

PREAMBLE	777
1. INTRODUCTION	779
1.1. Methodology and Evidence Review	779
1.2. Organization of the Writing Group	779
1.3. Document Review and Approval	779
6. INITIAL AND SERIAL EVALUATION OF THE HF PATIENT	780
6.3. Biomarkers	780
6.3.1. Biomarkers for Prevention: Recommendation	781
6.3.2. Biomarkers for Diagnosis: Recommendation	782
6.3.3. Biomarkers for Prognosis or Added Risk Stratification: Recommendations	782
7. TREATMENT OF STAGES A TO D	784
7.3. Stage C	784
7.3.2. Pharmacological Treatment for Stage C HF With Reduced Ejection Fraction: Recommendations	784
7.3.2.10. Renin-Angiotensin System Inhibition With Angiotensin-Converting Enzyme Inhibitor or Angiotensin Receptor Blocker or ARNI: Recommendations	784
7.3.2.11. Ivabradine: Recommendation	786
7.3.3. Pharmacological Treatment for Stage C HFpEF: Recommendations	789
9. IMPORTANT COMORBIDITIES IN HF	790
9.2. Anemia: Recommendations	790
9.5. Hypertension (New Section)	791
9.5.1. Treating Hypertension to Reduce the Incidence of HF: Recommendation	791

9.5.2. Treating Hypertension in Stage C HFrEF: Recommendation	791
9.5.3. Treating Hypertension in Stage C HFpEF: Recommendation	791
9.6. Sleep-Disordered Breathing: Recommendations ..	792

REFERENCES	793
-------------------------	-----

APPENDIX 1

Author Relationships With Industry and Other Entities (Relevant)	798
---	-----

APPENDIX 2

Reviewer Relationships With Industry and Other Entities (Comprehensive)	800
--	-----

APPENDIX 3

Abbreviations	803
----------------------------	-----

PREAMBLE

Since 1980, the American College of Cardiology (ACC) and American Heart Association (AHA) have translated scientific evidence into clinical practice guidelines (guidelines) with recommendations to improve cardiovascular health. These guidelines, which are based on systematic methods to evaluate and classify evidence, provide a cornerstone for quality cardiovascular care. The ACC and AHA sponsor the development and publication of guidelines without commercial support, and members of each organization volunteer their time to the writing and review efforts. Guidelines are official policy of the ACC and AHA.

Intended Use

Practice guidelines provide recommendations applicable to patients with or at risk of developing cardiovascular

disease. The focus is on medical practice in the United States, but guidelines developed in collaboration with other organizations may have a global impact. Although guidelines may be used to inform regulatory or payer decisions, their intent is to improve patients' quality of care and align with patients' interests. Guidelines are intended to define practices meeting the needs of patients in most, but not all, circumstances and should not replace clinical judgment.

Clinical Implementation

Guideline recommended management is effective only when followed by healthcare providers and patients. Adherence to recommendations can be enhanced by shared decision making between healthcare providers and patients, with patient engagement in selecting interventions based on individual values, preferences, and associated conditions and comorbidities.

Methodology and Modernization

The ACC/AHA Task Force on Clinical Practice Guidelines (Task Force) continuously reviews, updates, and modifies guideline methodology on the basis of published standards from organizations including the Institute of Medicine (1,2) and on the basis of internal reevaluation. Similarly, the presentation and delivery of guidelines are reevaluated and modified on the basis of evolving technologies and other factors to facilitate optimal dissemination of information at the point of care to healthcare professionals. Given time constraints of busy healthcare providers and the need to limit text, the current guideline format delineates that each recommendation be supported by limited text (ideally, <250 words) and hyperlinks to supportive evidence summary tables. Ongoing efforts to further limit text are underway. Recognizing the importance of cost-value considerations in certain guidelines, when appropriate and feasible, an analysis of the value of a drug, device, or intervention may be performed in accordance with the ACC/AHA methodology (3).

To ensure that guideline recommendations remain current, new data are reviewed on an ongoing basis, with full guideline revisions commissioned in approximately 6-year cycles. Publication of new, potentially practice-changing study results that are relevant to an existing or new drug, device, or management strategy will prompt evaluation by the Task Force, in consultation with the relevant guideline writing committee, to determine whether a focused update should be commissioned. For additional information and policies regarding guideline development, we encourage readers to consult the ACC/AHA guideline methodology manual (4) and other methodology articles (5-8).

Selection of Writing Committee Members

The Task Force strives to avoid bias by selecting experts from a broad array of backgrounds. Writing committee members represent different geographic regions, sexes, ethnicities, races, intellectual perspectives/biases, and scopes of clinical practice. The Task Force may also invite organizations and professional societies with related interests and expertise to participate as partners, collaborators, or endorsers.

Relationships With Industry and Other Entities

The ACC and AHA have rigorous policies and methods to ensure that guidelines are developed without bias or improper influence. The complete relationships with industry and other entities (RWI) policy can be found [online](#). [Appendix 1](#) of the current document lists writing committee members' relevant RWI. For the purposes of full transparency, writing committee members' comprehensive disclosure information is available [online](#). Comprehensive disclosure information for the Task Force is also available [online](#).

Evidence Review and Evidence Review Committees

When developing recommendations, the writing committee uses evidence-based methodologies that are based on all available data (4-7). Literature searches focus on randomized controlled trials (RCTs) but also include registries, nonrandomized comparative and descriptive studies, case series, cohort studies, systematic reviews, and expert opinion. Only key references are cited.

An independent evidence review committee (ERC) is commissioned when there are 1 or more questions deemed of utmost clinical importance that merit formal systematic review. This systematic review will strive to determine which patients are most likely to benefit from a drug, device, or treatment strategy and to what degree. Criteria for commissioning an ERC and formal systematic review include: a) the absence of a current authoritative systematic review, b) the feasibility of defining the benefit and risk in a time frame consistent with the writing of a guideline, c) the relevance to a substantial number of patients, and d) the likelihood that the findings can be translated into actionable recommendations. ERC members may include methodologists, epidemiologists, healthcare providers, and biostatisticians. When a formal systematic review has been commissioned, the recommendations developed by the writing committee on the basis of the systematic review are marked with "SR".

Guideline-Directed Management and Therapy

The term *guideline-directed management and therapy* (GDMT) encompasses clinical evaluation, diagnostic testing, and pharmacological and procedural treatments.

For these and all recommended drug treatment regimens, the reader should confirm the dosage by reviewing product insert material and evaluate the treatment regimen for contraindications and interactions. The recommendations are limited to drugs, devices, and treatments approved for clinical use in the United States.

Class of Recommendation and Level of Evidence

The Class of Recommendation (COR) indicates the strength of the recommendation, encompassing the estimated magnitude and certainty of benefit in proportion to risk. The Level of Evidence (LOE) rates the quality of scientific evidence that supports the intervention on the basis of the type, quantity, and consistency of data from clinical trials and other sources ([Table 1](#)) (4-6).

*Glenn N. Levine, MD, FACC, FAHA
Chair, ACC/AHA Task Force on Clinical
Practice Guidelines*

1. INTRODUCTION

The purpose of this focused update is to update the “2013 ACCF/AHA Guideline for the Management of Heart Failure” (9) (2013 HF guideline) in areas in which new evidence has emerged since its publication. For this update and future heart failure (HF) guidelines, the Heart Failure Society of America (HFSA) has partnered with the ACC and AHA to provide coordinated guidance on the management of HF.

The scope of the focused update includes revision to the sections on biomarkers; new therapies indicated for stage C HF with reduced ejection fraction (HFrEF); updates on HF with preserved ejection fraction (HFpEF); new data on important comorbidities, including sleep apnea, anemia, and hypertension; and new insights into the prevention of HF.

This focused update represents the second part of a 2-stage publication; with the first part having been published as the “2016 ACC/AHA/HFSA Focused Update on New Pharmacological Therapy for Heart Failure” (10), which introduced guidance on new therapies, specifically for the use of an angiotensin receptor-neprilysin inhibitor (ARNI) (valsartan/sacubitril) and a sinoatrial node modulator (ivabradine). That focused update was published concurrently with the European Society of Cardiology’s complete guideline, “2016 ESC Guidelines for the Diagnosis and Treatment of Acute and Chronic Heart Failure” (11).

1.1. Methodology and Evidence Review

To identify key data that influence guideline recommendations, the Task Force and members of the 2013 HF guideline writing committee reviewed clinical trials that were presented at the annual scientific meetings of the

ACC, AHA, and European Society of Cardiology and other scientific meetings and that were published in peer-reviewed format from April 2013 through November 2016. The evidence is summarized in tables in the [Online Data Supplement](#). All recommendations (new, modified, and unchanged) for each clinical section are included to provide a comprehensive assessment. The text explains new and modified recommendations, whereas recommendations from the previous guideline that have been deleted or superseded no longer appear. Please consult the full-text version of the 2013 HF guideline (9) for text and evidence tables supporting the unchanged recommendations and for clinical areas not addressed in this focused update. Individual recommendations in this focused update will be incorporated into the full-text guideline in the future. Recommendations from the prior guideline that remain current have been included for completeness, but the LOE reflects the COR/LOE system used when the recommendations were initially developed. New and modified recommendations in this focused update reflect the latest COR/LOE system, in which LOE B and C are subcategorized for greater specificity (4-6). The section numbers correspond to the full-text guideline sections.

1.2. Organization of the Writing Group

For this focused update, representative members of the 2013 HF guideline writing committee were invited to participate. They were joined by additional invited members to form a new writing group, which is referred to as the 2017 HF focused update writing group. Members were required to disclose all RWI relevant to the data under consideration. The group was composed of experts representing general cardiologists, HF and transplantation specialists, electrophysiologists, pharmacists, and general internists. The 2017 HF focused update writing group included representatives from the ACC, AHA, and HFSA, as well as the American Academy of Family Physicians, American College of Chest Physicians, American College of Physicians, and International Society for Heart and Lung Transplantation.

1.3. Document Review and Approval

The focused update was reviewed by 2 official reviewers each nominated by the ACC, AHA, and HFSA; 1 reviewer each from the American Academy of Family Physicians, American College of Chest Physicians, and International Society for Heart and Lung Transplantation; and 19 individual content reviewers. Reviewers’ RWI information is published in this document ([Appendix 2](#)).

This document was approved for publication by the governing bodies of the ACC, AHA, and HFSA.

TABLE 1 Applying Class of Recommendation and Level of Evidence to Clinical Strategies, Interventions, Treatments, or Diagnostic Testing in Patient Care* (Updated August 2015)

CLASS (STRENGTH) OF RECOMMENDATION		LEVEL (QUALITY) OF EVIDENCE†	
CLASS I (STRONG) Benefit >>> Risk		LEVEL A	
Suggested phrases for writing recommendations:		- High-quality evidence‡ from more than 1 RCT - Meta-analyses of high-quality RCTs - One or more RCTs corroborated by high-quality registry studies	
- Is recommended - Is indicated/useful/effective/beneficial - Should be performed/administered/other		LEVEL B-R (Randomized)	
Comparative-Effectiveness Phrases‡: - Treatment/strategy A is recommended/indicated in preference to treatment B - Treatment A should be chosen over treatment B		- Moderate-quality evidence‡ from 1 or more RCTs - Meta-analyses of moderate-quality RCTs	
CLASS IIa (MODERATE) Benefit >> Risk		LEVEL B-NR (Nonrandomized)	
Suggested phrases for writing recommendations:		- Moderate-quality evidence‡ from 1 or more well-designed, well-executed nonrandomized studies, observational studies, or registry studies - Meta-analyses of such studies	
- Is reasonable - Can be useful/effective/beneficial		LEVEL C-LD (Limited Data)	
Comparative-Effectiveness Phrases‡: - Treatment/strategy A is probably recommended/indicated in preference to treatment B - It is reasonable to choose treatment A over treatment B		- Randomized or nonrandomized observational or registry studies with limitations of design or execution - Meta-analyses of such studies - Physiological or mechanistic studies in human subjects	
CLASS IIb (WEAK) Benefit ≥ Risk		LEVEL C-EO (Expert Opinion)	
Suggested phrases for writing recommendations:		Consensus of expert opinion based on clinical experience	
- May/might be reasonable - May/might be considered - Usefulness/effectiveness is unknown/unclear/uncertain or not well established			
CLASS III: No Benefit (MODERATE) Benefit = Risk (Generally, LOE A or B use only)			
Suggested phrases for writing recommendations:			
- Is not recommended - Is not indicated/useful/effective/beneficial - Should not be performed/administered/other			
CLASS III: Harm (STRONG) Risk > Benefit			
Suggested phrases for writing recommendations:			
- Potentially harmful - Causes harm - Associated with excess morbidity/mortality - Should not be performed/administered/other			

COR and LOE are determined independently (any COR may be paired with any LOE).

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

* The outcome or result of the intervention should be specified (an improved clinical outcome or increased diagnostic accuracy or incremental prognostic information).

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

‡ The method of assessing quality is evolving, including the application of standardized, widely used, and preferably validated evidence grading tools; and for systematic reviews, the incorporation of an Evidence Review Committee.

COR indicates Class of Recommendation; EO, expert opinion; LD, limited data; LOE, Level of Evidence; NR, nonrandomized; R, randomized; and RCT, randomized controlled trial.

6. INITIAL AND SERIAL EVALUATION OF THE HF PATIENT

6.3. Biomarkers

Assays for BNP (B-type natriuretic peptide) and NT-proBNP (N-terminal pro-B-type natriuretic peptide), which are both natriuretic peptide biomarkers, have been used increasingly to establish the presence and severity of HF. In general, both natriuretic peptide biomarker values track similarly, and either can be used in patient care settings as long as their respective absolute values and cutpoints are not used interchangeably. Notably, BNP, but not NT-proBNP, is a substrate for neprilysin. Therefore, ARNI increases BNP levels (12) but not NT-proBNP levels (13). Note that the type of natriuretic peptide assay that has been performed must be considered

during interpretation of natriuretic peptide biomarker levels in patients on ARNI. In 2 studies with ARNI, NT-proBNP levels were reduced (12,14), with the reduction in 1 study being associated with improved clinical outcomes (12).

A substantial evidence base exists that supports the use of natriuretic peptide biomarkers to assist in the diagnosis or exclusion of HF as a cause of symptoms (e.g., dyspnea, weight gain) in the setting of chronic ambulatory HF (15–21) or in the setting of acute care with decompensated HF (22–30), especially when the cause of dyspnea is unclear. The role of natriuretic peptide biomarkers in population screening to detect incident HF is emerging (31–37). Elevated plasma levels of natriuretic peptide biomarkers are associated with a wide variety of cardiac and noncardiac causes (Table 2) (38–42). Obesity may be

associated with lower natriuretic peptide concentrations, and this may modestly reduce diagnostic sensitivity in morbidly obese patients (42).

Because of the absence of clear and consistent evidence for improvement in mortality and cardiovascular outcomes (43-62), there are insufficient data to inform specific guideline recommendations related to natriuretic peptide-guided therapy or serial measurements of BNP or NT-proBNP levels for the purpose of reducing hospitalization or deaths in the present document.

Like natriuretic peptides, cardiac troponin levels may be elevated in the setting of chronic or acute decompensated HF, suggesting myocyte injury or necrosis (63). Troponins I and T respond similarly for acute coronary syndromes and acute decompensated HF. Elevations in either troponin I or T levels in the setting of acute HF are of prognostic significance and must be interpreted in the clinical context (64).

In addition to natriuretic peptides and troponins (65-67), multiple other biomarkers, including those of inflammation, oxidative stress, vascular dysfunction, and myocardial and matrix remodeling, have been implicated in HF (68-71). Biomarkers of myocardial fibrosis, soluble ST2 receptor, and galectin-3 are predictive of hospitalization and death and may provide incremental prognostic value over natriuretic peptide levels in patients with HF (72-74). Strategies that combine multiple biomarkers may ultimately prove beneficial in guiding HF therapy in the future, but multicenter studies with larger derivation and validation cohorts are needed (75,76). Several emerging biomarkers await validation with well-defined outcome measures and prognostic accuracy before they can reach the clinical arena (77-84).

6.3.1. Biomarkers for Prevention: Recommendation

Biomarkers: Recommendation for Prevention of HF

COR	LOE	RECOMMENDATION	COMMENT/RATIONALE
Ila	B-R	For patients at risk of developing HF, natriuretic peptide biomarker-based screening followed by team-based care, including a cardiovascular specialist optimizing GDMT, can be useful to prevent the development of left ventricular dysfunction (systolic or diastolic) or new-onset HF (85,86).	NEW: New data suggest that natriuretic peptide biomarker screening and early intervention may prevent HF.

See Online Data Supplements A and B.

In a large-scale unblinded single-center study (STOP-HF [The St Vincent's Screening to Prevent Heart Failure]) (85), patients at risk of HF (identified by the presence of hypertension, diabetes mellitus, or known vascular disease [e.g., stage A HF]), but without established left ventricular systolic dysfunction or symptomatic HF at baseline, were randomly assigned to receive screening with BNP testing or usual primary care. Intervention-group participants with BNP levels of ≥ 50 pg/mL underwent echocardiography and were referred to a cardiovascular specialist who decided on further investigation and management. All patients received further coaching by a specialist nurse who emphasized individual risk and the importance of adherence to medication and healthy lifestyle behaviors. BNP-based screening reduced the composite endpoint of asymptomatic left ventricular dysfunction (systolic or diastolic) with or without newly diagnosed HF (85). Similarly, in another small, single-center RCT, accelerated up-titration of renin-angiotensin-aldosterone system antagonists and beta blockers reduced cardiac events in patients with diabetes mellitus and elevated NT-proBNP levels but without cardiac disease at baseline (86). Developing a standardized strategy to screen and intervene in patients at risk of HF can be difficult because of different definitions of HF risk, heterogeneity of prevalence in different populations, variable duration until clinical HF or left ventricular dysfunction develops, and variable interventions for risk factor modification or treatment. Further studies are needed to determine cost-effectiveness and risk of such screening, as well as its impact on quality of life (QoL) and mortality rate.

TABLE 2 Selected Potential Causes of Elevated Natriuretic Peptide Levels (38-41)

Cardiac

HF, including RV syndromes
Acute coronary syndromes
Heart muscle disease, including LVH
Valvular heart disease
Pericardial disease
Atrial fibrillation
Myocarditis
Cardiac surgery
Cardioversion
Toxic-metabolic myocardial insults, including cancer chemotherapy

Noncardiac

Advancing age
Anemia
Renal failure
Pulmonary: obstructive sleep apnea, severe pneumonia
Pulmonary hypertension
Critical illness
Bacterial sepsis
Severe burns

Modified from Table 8 of the 2013 HF guideline (9).

HF, indicates heart failure; LVH, left ventricular hypertrophy; and RV, right ventricular.

This section categorizes the role of biomarkers into prevention, diagnosis, prognosis, and added risk stratification to clarify evidence-based objectives of their use in clinical practice.

6.3.2. Biomarkers for Diagnosis: Recommendation

Biomarkers: Recommendation for Diagnosis

COR	LOE	RECOMMENDATION	COMMENT/RATIONALE
I	A	In patients presenting with dyspnea, measurement of natriuretic peptide biomarkers is useful to support a diagnosis or exclusion of HF (15-24,28-30).	MODIFIED: 2013 acute and chronic recommendations have been combined into a diagnosis section.
See Online Data Supplements A and B.			

Natriuretic peptide biomarker testing in the setting of chronic ambulatory HF provides incremental diagnostic value to clinical judgment, especially when the etiology of dyspnea is unclear (15-21). In emergency settings, natriuretic peptide biomarker levels usually have higher sensitivity than specificity and may be more useful for ruling out than ruling in HF (20). Although lower values of natriuretic peptide biomarkers 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 2) (38-41).

6.3.3. Biomarkers for Prognosis or Added Risk Stratification: Recommendations

Biomarkers: Recommendations for Prognosis

COR	LOE	RECOMMENDATIONS	COMMENT/RATIONALE
I	A	Measurement of BNP or NT-proBNP is useful for establishing prognosis or disease severity in chronic HF (16,87-92).	2013 recommendation remains current.
I	A	Measurement of baseline levels of natriuretic peptide biomarkers and/or cardiac troponin on admission to the hospital is useful to establish a prognosis in acutely decompensated HF (27,93-100).	MODIFIED: Current recommendation emphasizes that it is admission levels of natriuretic peptide biomarkers that are useful.
See Online Data Supplements A and B.			

Higher levels of natriuretic peptide biomarkers on admission are usually associated with greater risk for clinical outcomes, including all-cause and cardiovascular mortality, morbidity, and composite outcomes, across different time intervals in patients with decompensated HF (20,27,29,93-101). Similarly, abnormal levels of circulating cardiac troponin are commonly found in patients with acute decompensated HF, often without obvious myocardial ischemia or underlying coronary artery disease (CAD), and this is associated with worse clinical outcomes and higher risk of death (95,99,102,103).

Studies have demonstrated incremental prognostic value of these biomarkers to standard approaches of cardiovascular disease risk assessment (29,95). However, there were differences in the risk prediction models, assay cutpoints, and lengths of follow-up (29). Furthermore, not all patients may need biomarker measurement for prognostication, especially if they already have advanced HF with established poor prognosis or persistently elevated levels of biomarkers in former settings. Therefore, assays of natriuretic peptide biomarkers for incremental prognostication should not preclude good clinical judgment; an individualized approach to each patient is paramount.

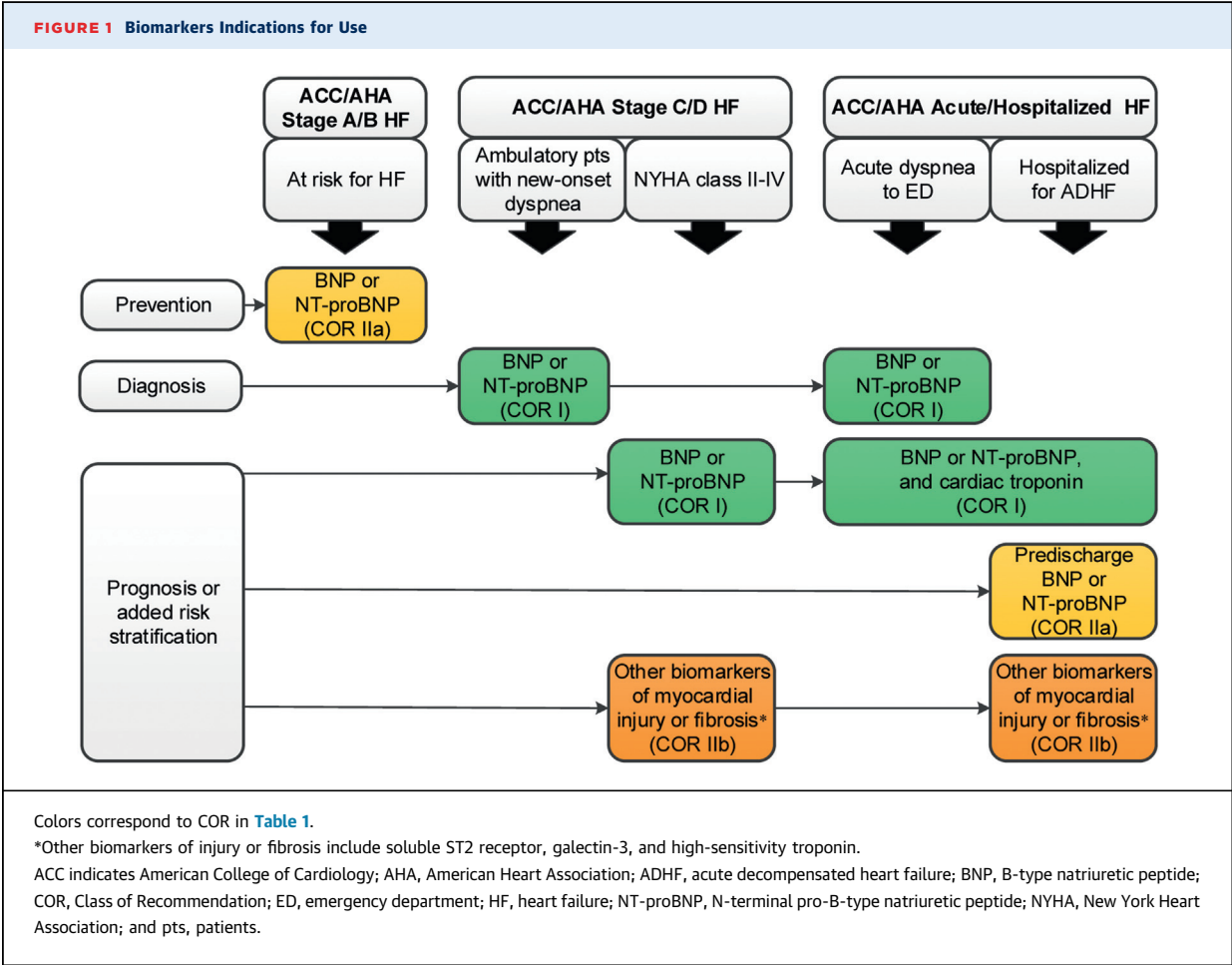
Ila	B-NR	During a HF hospitalization, a predischage natriuretic peptide level can be useful to establish a postdischarge prognosis (93,96,104-113).	NEW: Current recommendation reflects new observational studies.
See Online Data Supplements A and B.			

Predischage natriuretic peptide biomarker levels and the relative change in levels during hospital treatment are strong predictors of the risk of death or hospital readmission for HF (93,96,104-113). Several studies have suggested that predischage natriuretic peptide biomarker levels had higher reclassification and discrimination value than clinical variables in predicting outcomes (96,106,108-111). Patients with higher predischage levels and patients who do not have a decrease in natriuretic peptide biomarker levels during hospitalization have worse outcomes (96,106,108-111). Although observational or retrospective studies have suggested that patients with natriuretic peptide biomarker reduction had better outcomes than those without any changes or with a biomarker rise (93,107,112,113), targeting a certain threshold, value, or relative change in these biomarker levels during hospitalization may not be practical or safe for every patient and has not been tested in a prospective large-scale trial. Clinical assessment and adherence to GDMT should be the emphasis, and the prognostic value of a predischage value or relative changes does not imply the necessity for serial and repeated biomarker measurements during hospitalization.

(continued)

IIb	B-NR	In patients with chronic HF, measurement of other clinically available tests, such as biomarkers of myocardial injury or fibrosis, may be considered for additive risk stratification (27,95,98,99,103,114-119).	MODIFIED: 2013 recommendations have been combined into prognosis section, resulting in LOE change from A to B-NR.
See Online Data Supplements A and B.			

Biomarkers of myocardial fibrosis (e.g., soluble ST2 receptor, galectin-3, high-sensitivity cardiac troponin, and others) are predictive of hospitalization and death in patients with HF and also are additive to natriuretic peptide biomarker levels in their prognostic value (117,119-126). A combination of biomarkers may ultimately prove to be more informative than single biomarkers (127).



7. TREATMENT OF STAGES A TO D

7.3. Stage C

7.3.2. Pharmacological Treatment for Stage C HF With Reduced Ejection Fraction: Recommendations

(See [Figure 2](#) and [Table 3](#)).

7.3.2.10. Renin-Angiotensin System Inhibition With Angiotensin-Converting Enzyme Inhibitor or Angiotensin Receptor Blocker or ARNI: Recommendations

Recommendations for Renin-Angiotensin System Inhibition With ACE Inhibitor or ARB or ARNI

COR	LOE	RECOMMENDATIONS	COMMENT/RATIONALE
I	ACE-I: A ARB: A	The clinical strategy of inhibition of the renin-angiotensin system with ACE inhibitors (<i>Level of Evidence: A</i>) (128-133), <u>OR</u> ARBs (<i>Level of Evidence: A</i>) (134-137), <u>OR</u> ARNI (<i>Level of Evidence: B-R</i>) (138) in conjunction with evidence-based beta blockers (9,139,140), and aldosterone antagonists in selected patients (141,142), is recommended for patients with chronic HFrEF to reduce morbidity and mortality.	NEW: New clinical trial data prompted clarification and important updates.
	ARNI: B-R		
See Online Data Supplements 1, 2, 18-20.			
Angiotensin-converting enzyme (ACE) inhibitors reduce morbidity and mortality in heart failure with reduced ejection fraction (HFrEF). Randomized controlled trials (RCTs) clearly establish the benefits of ACE inhibition in patients with mild, moderate, or severe symptoms of HF and in patients with or without coronary artery disease (128-133). ACE inhibitors can produce angioedema and should be given with caution to patients with low systemic blood pressures, renal insufficiency, or elevated serum potassium. ACE inhibitors also inhibit kininase and increase levels of bradykinin, which can induce cough but also may contribute to their beneficial effect through vasodilation. Angiotensin receptor blockers (ARBs) were developed with the rationale that angiotensin II production continues in the presence of ACE inhibition, driven through alternative enzyme pathways. ARBs do not inhibit kininase and are associated with a much lower incidence of cough and angioedema than ACE inhibitors; but like ACE inhibitors, ARBs should be given with caution to patients with low systemic blood pressure, renal insufficiency, or elevated serum potassium. Long-term therapy with ARBs produces hemodynamic, neurohormonal, and clinical effects consistent with those expected after interference with the renin-angiotensin system and have been shown in RCTs (134-137) to reduce morbidity and mortality, especially in ACE inhibitor-intolerant patients. In ARNI, an ARB is combined with an inhibitor of neprilysin, an enzyme that degrades natriuretic peptides, bradykinin, adrenomedullin, and other vasoactive peptides. In an RCT that compared the first approved ARNI, valsartan/sacubitril, with enalapril in symptomatic patients with HFrEF tolerating an adequate dose of either ACE inhibitor or ARB, the ARNI reduced the composite endpoint of cardiovascular death or HF hospitalization significantly, by 20% (138). The benefit was seen to a similar extent for both death and HF hospitalization and was consistent across subgroups. The use of ARNI is associated with the risk of hypotension and renal insufficiency and may lead to angioedema, as well.			
I	ACE-I: A	The use of ACE inhibitors is beneficial for patients with prior or current symptoms of chronic HFrEF to reduce morbidity and mortality (128-133,143).	2013 recommendation repeated for clarity in this section.
See Online Data Supplement 18.			
ACE inhibitors have been shown in large RCTs to reduce morbidity and mortality in patients with HFrEF with mild, moderate, or severe symptoms of HF, with or without coronary artery disease (128-133). Data suggest that there are no differences among available ACE inhibitors in their effects on symptoms or survival (143). ACE inhibitors should be started at low doses and titrated upward to doses shown to reduce the risk of cardiovascular events in clinical trials. ACE inhibitors can produce angioedema and should be given with caution to patients with low systemic blood pressures, renal insufficiency, or elevated serum potassium (>5.0 mEq/L). Angioedema occurs in <1% of patients who take an ACE inhibitor, but it occurs more frequently in blacks and women (144). Patients should not be given ACE inhibitors if they are pregnant or plan to become pregnant. ACE inhibitors also inhibit kininase and increase levels of bradykinin, which can induce cough in up to 20% of patients but also may contribute to beneficial vasodilation. If maximal doses are not tolerated, intermediate doses should be tried; abrupt withdrawal of ACE inhibition can lead to clinical deterioration and should be avoided. Although the use of an ARNI in lieu of an ACE inhibitor for HFrEF has been found to be superior, <i>for those patients for whom ARNI is not appropriate, continued use of an ACE inhibitor for all classes of HFrEF remains strongly advised.</i>			

(continued)

I	ARB: A	The use of ARBs to reduce morbidity and mortality is recommended in patients with prior or current symptoms of chronic HFrEF who are intolerant to ACE inhibitors because of cough or angioedema (134-137,145,146).	2013 recommendation repeated for clarity in this section.
See Online Data Supplements 2 and 19.		ARBs have been shown to reduce mortality and HF hospitalizations in patients with HFrEF in large RCTs (134-137). Long-term therapy with ARBs in patients with HFrEF produces hemodynamic, neurohormonal, and clinical effects consistent with those expected after interference with the renin-angiotensin system (145,146). Unlike ACE inhibitors, ARBs do not inhibit kininase and are associated with a much lower incidence of cough and angioedema, although kininase inhibition by ACE inhibitors may produce beneficial vasodilatory effects. Patients intolerant to ACE inhibitors because of cough or angioedema should be started on ARBs; patients already tolerating ARBs for other indications may be continued on ARBs if they subsequently develop HF. ARBs should be started at low doses and titrated upward, with an attempt to use doses shown to reduce the risk of cardiovascular events in clinical trials. ARBs should be given with caution to patients with low systemic blood pressure, renal insufficiency, or elevated serum potassium (>5.0 mEq/L). Although ARBs are alternatives for patients with ACE inhibitor-induced angioedema, caution is advised because some patients have also developed angioedema with ARBs. Head-to-head comparisons of an ARB versus ARNI for HF do not exist. <i>For those patients for whom an ACE inhibitor or ARNI is inappropriate, use of an ARB remains advised.</i>	
I	ARNI: B-R	In patients with chronic symptomatic HFrEF NYHA class II or III who tolerate an ACE inhibitor or ARB, replacement by an ARNI is recommended to further reduce morbidity and mortality (138).	NEW: New clinical trial data necessitated this recommendation.
See Online Data Supplements 1 and 18.		Benefits of ACE inhibitors with regard to decreasing HF progression, hospitalizations, and mortality rate have been shown consistently for patients across the clinical spectrum, from asymptomatic to severely symptomatic HF. Similar benefits have been shown for ARBs in populations with mild-to-moderate HF who are unable to tolerate ACE inhibitors. In patients with mild-to-moderate HF (characterized by either 1) mildly elevated natriuretic peptide levels, BNP [B-type natriuretic peptide] >150 pg/mL or NT-proBNP [N-terminal pro-B-type natriuretic peptide] ≥600 pg/mL; or 2) BNP ≥100 pg/mL or NT-proBNP ≥400 pg/mL with a prior hospitalization in the preceding 12 months) who were able to tolerate both a target dose of enalapril (10 mg twice daily) and then subsequently an ARNI (valsartan/sacubitril; 200 mg twice daily, with the ARB component equivalent to valsartan 160 mg), hospitalizations and mortality were significantly decreased with the valsartan/sacubitril compound compared with enalapril. The target dose of the ACE inhibitor was consistent with that known to improve outcomes in previous landmark clinical trials (129). This ARNI has been approved for patients with symptomatic HFrEF and is intended to be substituted for ACE inhibitors or ARBs. HF effects and potential off-target effects may be complex with inhibition of the neprilysin enzyme, which has multiple biological targets. Use of an ARNI is associated with hypotension and a low-frequency incidence of angioedema. To facilitate initiation and titration, the approved ARNI is available in 3 doses that include a dose that was not tested in the HF trial; the target dose used in the trial was 97/103 mg twice daily (147). Clinical experience will provide further information about the optimal titration and tolerability of ARNI, particularly with regard to blood pressure, adjustment of concomitant HF medications, and the rare complication of angioedema (14).	
III: Harm	B-R	ARNI should not be administered concomitantly with ACE inhibitors or within 36 hours of the last dose of an ACE inhibitor (148,149).	NEW: Available evidence demonstrates a potential signal of harm for a concomitant use of ACE inhibitors and ARNI.
See Online Data Supplement 3.		Oral neprilysin inhibitors, used in combination with ACE inhibitors can lead to angioedema and concomitant use is contraindicated and should be avoided. A medication that represented both a neprilysin inhibitor and an ACE inhibitor, omapatrilat, was studied in both hypertension and HF, but its development was terminated because of an unacceptable incidence of angioedema (148,149) and associated significant morbidity. This adverse effect was thought to occur because both ACE and neprilysin break down bradykinin, which directly or indirectly can cause angioedema (149,150). An ARNI should not be administered within 36 hours of switching from or to an ACE inhibitor.	

(continued)

III: Harm	C-EO	ARNI should not be administered to patients with a history of angioedema.	NEW: New clinical trial data.
N/A		Omapatrilat, a neprilysin inhibitor (as well as an ACE inhibitor and aminopeptidase P inhibitor), was associated with a higher frequency of angioedema than that seen with enalapril in an RCT of patients with HFrEF (148). In a very large RCT of hypertensive patients, omapatrilat was associated with a 3-fold increased risk of angioedema as compared with enalapril (149). Blacks and smokers were particularly at risk. The high incidence of angioedema ultimately led to cessation of the clinical development of omapatrilat (151,152). In light of these observations, angioedema was an exclusion criterion in the first large trial assessing ARNI therapy in patients with hypertension (153) and then in the large trial that demonstrated clinical benefit of ARNI therapy in HFrEF (138). ARNI therapy should not be administered in patients with a history of angioedema because of the concern that it will increase the risk of a recurrence of angioedema.	

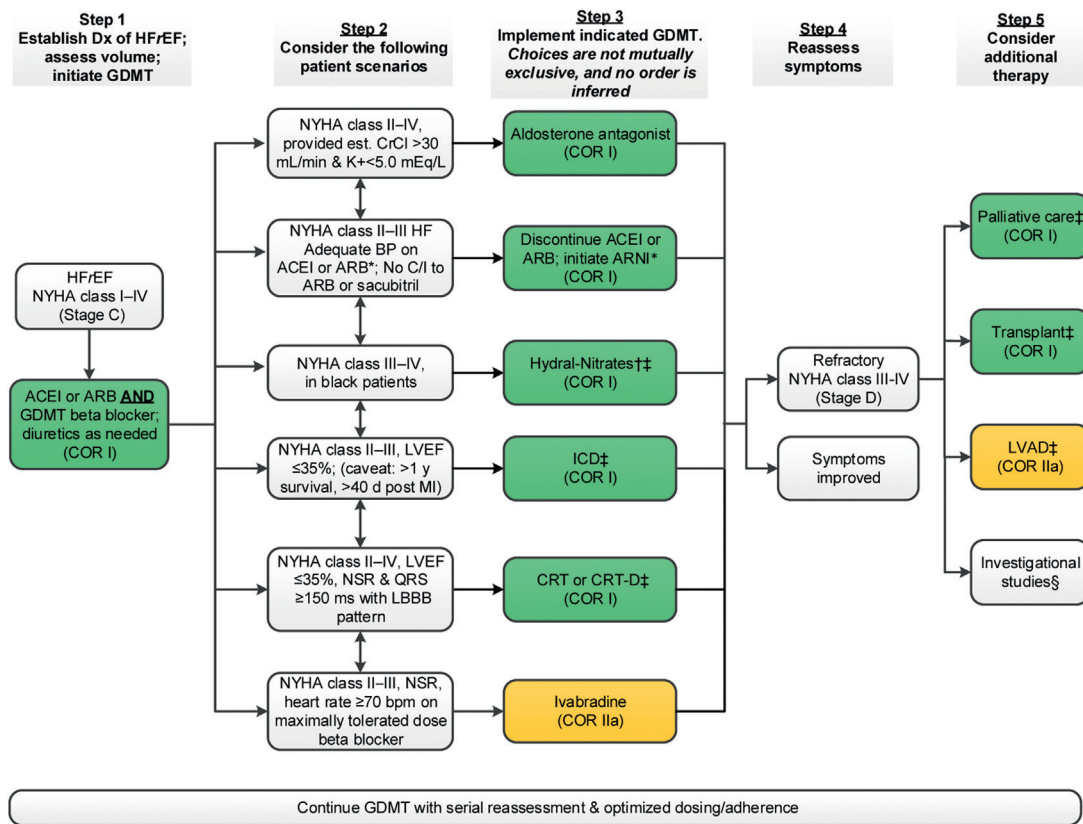
7.3.2.11. Ivabradine: Recommendation

Recommendation for Ivabradine

COR	LOE	RECOMMENDATION	COMMENT/RATIONALE
IIa	B-R	Ivabradine can be beneficial to reduce HF hospitalization for patients with symptomatic (NYHA class II-III) stable chronic HFrEF (LVEF $\leq$35%) who are receiving GDEM*, including a beta blocker at maximum tolerated dose, and who are in sinus rhythm with a heart rate of 70 bpm or greater at rest (154-157).	NEW: New clinical trial data.
See Online Data Supplement 4.		Ivabradine is a new therapeutic agent that selectively inhibits the I_f current in the sinoatrial node, providing heart rate reduction. One RCT demonstrated the efficacy of ivabradine in reducing the composite endpoint of cardiovascular death or HF hospitalization (155). The benefit of ivabradine was driven by a reduction in HF hospitalization. The study included patients with HFrEF (NYHA class II-IV, albeit with only a modest representation of NYHA class IV HF) and left ventricular ejection fraction (LVEF) $\leq$35%, in sinus rhythm with a resting heart rate of $\geq$70 beats per minute. Patients enrolled included a small number with paroxysmal atrial fibrillation (<40% of the time) but otherwise in sinus rhythm and a small number experiencing ventricular pacing but with a predominant sinus rhythm. Those with a myocardial infarction within the preceding 2 months were excluded. Patients enrolled had been hospitalized for HF in the preceding 12 months and were on stable GDEM* for 4 weeks before initiation of ivabradine therapy. The target of ivabradine is heart rate slowing (the presumed benefit of action), but only 25% of patients studied were on optimal doses of beta-blocker therapy (9,139,140,155). Given the well-proven mortality benefits of beta-blocker therapy, it is important to initiate and up titrate these agents to target doses, as tolerated, before assessing the resting heart rate for consideration of ivabradine initiation (155).	

*In other parts of the document, the term "GDMT" has been used to denote guideline-directed management and therapy. In this recommendation, however, the term "GDEM" has been used to denote this same concept in order to reflect the original wording of the recommendation that initially appeared in the "2016 ACC/AHA/HFSA Focused Update on New Pharmacological Therapy for Heart Failure: An Update of the 2013 ACCF/AHA Guideline for the Management of Heart Failure" (10).

FIGURE 2 Treatment of HFrEF Stage C and D



Colors correspond to COR in Table 1. For all medical therapies, dosing should be optimized and serial assessment exercised.

*See text for important treatment directions.

†Hydral-Nitrates green box: The combination of ISDN/HYD with ARNI has not been robustly tested. BP response should be carefully monitored. ‡See 2013 HF guideline (9).

§Participation in investigational studies is also appropriate for stage C, NYHA class II and III HF.

ACEI indicates angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor-blocker; ARNI, angiotensin receptor-neprilysin inhibitor; BP, blood pressure; bpm, beats per minute; C/I, contraindication; COR, Class of Recommendation; CrCl, creatinine clearance; CRT-D, cardiac resynchronization therapy-device; Dx, diagnosis; GDMT, guideline-directed management and therapy; HF, heart failure; HFrEF, heart failure with reduced ejection fraction; ICD, implantable cardioverter-defibrillator; ISDN/HYD, isosorbide dinitrate hydral-nitrates; K⁺, potassium; LBBB, left bundle-branch block; LVAD, left ventricular assist device; LVEF, left ventricular ejection fraction; MI, myocardial infarction; NSR, normal sinus rhythm; and NYHA, New York Heart Association.

TABLE 3 Drugs Commonly Used for HFrEF (Stage C HF)

Drug	Initial Daily Dose(s)	Maximum Doses(s)	Mean Doses Achieved in Clinical Trials	References
ACE inhibitors				
Captopril	6.25 mg TID	50 mg TID	122.7 mg QD	(158)
Enalapril	2.5 mg BID	10-20 mg BID	16.6 mg QD	(129)
Fosinopril	5-10 mg QD	40 mg QD	N/A	—
Lisinopril	2.5-5 mg QD	20-40 mg QD	32.5-35.0 mg QD	(130)
Perindopril	2 mg QD	8-16 mg QD	N/A	—
Quinapril	5 mg BID	20 mg BID	N/A	—
Ramipril	1.25-2.5 mg QD	10 mg QD	N/A	—
Trandolapril	1 mg QD	4 mg QD	N/A	—
ARBs				
Candesartan	4-8 mg QD	32 mg QD	24 mg QD	(137)
Losartan	25-50 mg QD	50-150 mg QD	129 mg QD	(136)
Valsartan	20-40 mg BID	160 mg BID	254 mg QD	(134)
ARNI				
Sacubitril/valsartan	49/51 mg BID (sacubitril/valsartan) (therapy may be initiated at 24/26 mg BID)	97/103 mg BID (sacubitril/valsartan)	375 mg QD; target dose: 24/26 mg, 49/51 mg OR 97/103 mg BID	(138)
I_f channel inhibitor				
Ivabradine	5 mg BID	7.5 mg BID	6.4 mg BID (at 28 d) 6.5 mg BID (at 1 y)	(155-157)
Aldosterone antagonists				
Spironolactone	12.5-25 mg QD	25 mg QD or BID	26 mg QD	(142)
Eplerenone	25 mg QD	50 mg QD	42.6 mg QD	(159)
Beta blockers				
Bisoprolol	1.25 mg QD	10 mg QD	8.6 mg QD	(160)
Carvedilol	3.125 mg BID	50 mg BID	37 mg QD	(161)
Carvedilol CR	10 mg QD	80 mg QD	N/A	—
Metoprolol succinate extended release (metoprolol CR/XL)	12.5-25 mg QD	200 mg QD	159 mg QD	(139)
Isosorbide dinitrate and hydralazine				
Fixed-dose combination	20 mg isosorbide dinitrate/ 37.5 mg hydralazine TID	40 mg isosorbide dinitrate/ 75 mg hydralazine TID	90 mg isosorbide dinitrate/ ~175 mg hydralazine QD	(162)
Isosorbide dinitrate and hydralazine	20-30 mg isosorbide dinitrate/ 25-50 mg hydralazine TID or QD	40 mg isosorbide dinitrate TID with 100 mg hydralazine TID	N/A	(163)

Modified (Table 15) from the 2013 HF guideline (9).

ACE indicates angiotensin-converting enzyme; ARB, angiotensin receptor blocker; ARNI, angiotensin receptor-neprilysin inhibitor; BID, twice daily; CR, controlled release; CR/XL, controlled release/extended release; HF, heart failure; HFrEF, heart failure with reduced ejection fraction; N/A, not applicable; QD, once daily; and TID, 3 times daily.

7.3.3. Pharmacological Treatment for Stage C HFpEF: Recommendations

Recommendations for Stage C HFpEF

COR	LOE	RECOMMENDATIONS	COMMENT/RATIONALE
I	B	Systolic and diastolic blood pressure should be controlled in patients with HFpEF in accordance with published clinical practice guidelines to prevent morbidity (164,165).	2013 recommendation remains current.
I	C	Diuretics should be used for relief of symptoms due to volume overload in patients with HFpEF.	2013 recommendation remains current.
Ila	C	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 HFpEF despite GDMT.	2013 recommendation remains current.
Ila	C	Management of AF according to published clinical practice guidelines in patients with HFpEF is reasonable to improve symptomatic HF.	2013 recommendation remains current (Section 9.1 in the 2013 HF guideline).
Ila	C	The use of beta-blocking agents, ACE inhibitors, and ARBs in patients with hypertension is reasonable to control blood pressure in patients with HFpEF.	2013 recommendation remains current.
Iib	B-R	In appropriately selected patients with HFpEF (with EF $\geq$ 45%, elevated BNP levels or HF admission within 1 year, estimated glomerular filtration rate $>$ 30 mL/min, creatinine $<$ 2.5 mg/dL, potassium $<$ 5.0 mEq/L), aldosterone receptor antagonists might be considered to decrease hospitalizations (83,166,167).	NEW: Current recommendation reflects new RCT data.
See Online Data Supplement C.			
Mechanistic studies have suggested that mineralocorticoid receptor antagonists can improve measures of diastolic function in patients with HFpEF, possibly by a similar effect on remodeling (83,168). The TOPCAT (Treatment of Preserved Cardiac Function Heart Failure With an Aldosterone Antagonist) trial (166) investigated the effects of spironolactone on a combined endpoint of death, aborted cardiac death, and HF hospitalization in patients with HFpEF. A small reduction (HR=0.89) in this composite endpoint did not reach statistical significance, although HF hospitalization was reduced (HR=0.83); known side effects of hyperkalemia and rising creatinine were seen more commonly in the treatment group (166). An unusual amount of regional variation was seen in this trial, prompting a post-hoc analysis (167) that showed that rates of the primary endpoint were 4-fold lower in Russia/Georgia than in North America and South America (the Americas). Rates in the Americas were comparable to those in other HFpEF trials (169,170). The post-hoc analysis showed efficacy in the Americas (HR=0.83) but not in Russia/Georgia (HR=1.10). Moreover, a sample of the Russia/Georgia population, despite having been in the active treatment arm, had nondetectable levels of the metabolite of spironolactone. These post-hoc analyses have significant limitations, but they suggest that in appropriately selected patients with symptomatic HFpEF (with ejection fraction [EF] $\geq$45%, elevated BNP level or HF admission within 1 year, estimated glomerular filtration rate $>$30 mL/min creatinine $<$2.5 mg/dL, and potassium $<$5.0 mEq/L), particularly in those with elevated BNP levels, use of spironolactone might be considered with close monitoring of potassium and renal function. Confirmatory studies are required. With regard to the use of mineralocorticoid receptor antagonists, creatinine should be $<$2.5 mg/dL in men or $<$2.0 mg/dL in women (or estimated glomerular filtration rate $>$30 mL/min) and potassium should be $<$5.0 mEq/L. Careful monitoring of potassium, renal function, and diuretic dosing represents best practices at initiation and during follow-up thereafter to minimize risk of hyperkalemia and worsening renal function.			
Iib	B	The use of ARBs might be considered to decrease hospitalizations for patients with HFpEF (169).	2013 recommendation remains current.
III: No Benefit	B-R	Routine use of nitrates or phosphodiesterase-5 inhibitors to increase activity or QoL in patients with HFpEF is ineffective (171,172).	NEW: Current recommendation reflects new data from RCTs.
See Online Data Supplement C.			

(continued)

Nitrate therapy can reduce pulmonary congestion and improve exercise tolerance in patients with HFrEF. However, the NEAT-HFpEF (Nitrate's Effect on Activity Tolerance in Heart Failure With Preserved Ejection Fraction) trial (171) randomized 110 patients with EF $\geq$ 50% on stable HF therapy, not including nitrates, and with activity limited by dyspnea, fatigue, or chest pain, to either isosorbide mononitrate or placebo and found no beneficial effects on activity levels, QoL, exercise tolerance, or NT-proBNP levels. On the basis of this trial, routine use of nitrates in patients with HFpEF is not recommended. This recommendation does not apply to patients with HFpEF and symptomatic CAD for whom nitrates may provide symptomatic relief. Phosphodiesterase-5 inhibition augments the nitric oxide system by upregulating cGMP activity. The RELAX (Phosphodiesterase-5 Inhibition to Improve Clinical Status and Exercise Capacity in Heart Failure with Preserved Ejection Fraction) trial (172) randomized 216 patients with EF $\geq$ 50% on stable HF therapy and with reduced exercise tolerance (peak observed Vo_2 $<$ 60% of predicted) to phosphodiesterase-5 inhibition with sildenafil or placebo. This study did not show improvement in oxygen consumption or exercise tolerance.

III: No Benefit	C	Routine use of nutritional supplements is not recommended for patients with HFpEF.	2013 recommendation remains current.
-----------------	---	--	--------------------------------------

9. IMPORTANT COMORBIDITIES IN HF

9.2. Anemia: Recommendations

Recommendations for Anemia

COR	LOE	RECOMMENDATIONS	COMMENT/RATIONALE
IIb See Online Data Supplement D.	B-R	In patients with NYHA class II and III HF and iron deficiency (ferritin $<$ 100 ng/mL or 100 to 300 ng/mL if transferrin saturation is $<$ 20%), intravenous iron replacement might be reasonable to improve functional status and QoL (173,174).	NEW: New evidence consistent with therapeutic benefit.

Routine baseline assessment of all patients with HF includes an evaluation for anemia in addition to other baseline laboratory measurements. Anemia is independently associated with HF disease severity, and iron deficiency appears to be uniquely associated with reduced exercise capacity. When iron deficiency is diagnosed and after full evaluation for cause, intravenous repletion of iron, especially in the setting of concomitant hepcidin deficiency in HF, may improve exercise capacity and QoL. Studies examining correction of iron deficiency in HF have demonstrated improvement in surrogate endpoints, such as QoL, NT-proBNP, and LVEF; however, controlled trials have been underpowered to detect reductions in hard clinical endpoints. The FAIR-HF (Ferric Carboxymaltose Assessment in Patients With Iron Deficiency and Chronic Heart Failure) trial (173) demonstrated improvements in NYHA class and functional capacity over a short-term exposure. The CONFIRM-HF (Ferric Carboxymaltose Evaluation on Performance in Patients With Iron Deficiency in Combination with Chronic Heart Failure) trial (174) included a larger cohort of patients ($n=304$) and demonstrated improvements in 6-minute walk test. A meta-analysis of 5 prospective controlled studies (631 patients) evaluated the effect of intravenous iron on deaths, hospitalizations, and other events in patients with HF and iron deficiency (175). Patients receiving intravenous iron experienced limited but statistically significant improvements in functional capacity and LVEF but no reduction in mortality rate. The FAIR-HF 2 trial is underway to further address the potential benefit of intravenous iron in HF associated with iron deficiency. Therefore, a strong recommendation for intravenous iron repletion must await the results of an appropriately powered trial on morbidity and mortality. There is an uncertain evidence base for oral iron repletion in the setting of anemia associated with HF.

III: No Benefit See Online Data Supplement D.	B-R	In patients with HF and anemia, erythropoietin-stimulating agents should not be used to improve morbidity and mortality (176).	NEW: Current recommendation reflects new evidence demonstrating absence of therapeutic benefit.
--	-----	--	--

Small studies evaluating the treatment of anemia in patients with HF have suggested a trend toward improvement in functional capacity and reduction in hospitalization with the use of erythropoietin-stimulating agents (177-182), but results have varied (183) and have been limited because of sample size. Although a meta-analysis of 11 RCTs ($n=794$) comparing erythropoietin-stimulating agents to control in patients with HF demonstrated significant improvements in 6-minute walk, exercise duration, peak Vo_2 , NYHA functional status, EF, BNP, HF-related hospitalizations, and QoL (184), in the STAMINA-HeFT (Study of Anemia in Heart Failure) trial (183), darbepoetin alfa was not associated with significant clinical benefits. In the largest RCT to date ($n=2,278$), correction of anemia with darbepoetin alfa did not result in benefit and resulted in a significant increase in the risk of thromboembolic events and a nonsignificant increase in fatal and nonfatal strokes, supporting findings from other trials (176,185-188). In summary, the strongest evidence on erythropoietin-stimulating agent therapy in HF suggests lack of benefit and increased adverse events. Therefore, erythropoietin-stimulating agent therapy cannot be recommended in patients with HF and anemia.

9.5. Hypertension (New Section)

9.5.1. Treating Hypertension to Reduce the Incidence of HF: Recommendation

Recommendation for Prevention

COR	LOE	RECOMMENDATIONS	COMMENT/RATIONALE
I	B-R	In patients at increased risk, stage A HF, the optimal blood pressure in those with hypertension should be less than 130/80 mm Hg (189-193).	NEW: Recommendation reflects new RCT data.
See Online Data Supplements E and F.			
A large RCT demonstrated that in those with increased cardiovascular risk (defined as age >75 years, established vascular disease, chronic renal disease, or a Framingham Risk Score >15%), control of blood pressure to a goal systolic pressure of <120 mm Hg, as determined by blood pressure assessment as per research protocol, was associated with a significant reduction in the incidence of HF (191) and an overall decrease in cardiovascular death. Blood pressure measurements as generally taken in the office setting are typically 5 to 10 mm Hg higher than research measurements; thus, the goal of <130/80 mm Hg is an approximation of the target blood pressure in conventional practice. <i>Targeting a significant reduction in systolic blood pressure in those at increased risk for cardiovascular disease is a novel strategy to prevent HF.</i>			

9.5.2. Treating Hypertension in Stage C HFrEF: Recommendation

Recommendation for Hypertension in Stage C HFrEF

COR	LOE	RECOMMENDATION	COMMENT/RATIONALE
I	C-EO	Patients with HFrEF and hypertension should be prescribed GDMT titrated to attain systolic blood pressure less than 130 mm Hg (191).	NEW: Recommendation has been adapted from recent clinical trial data but not specifically tested per se in a randomized trial of patients with HF.
See Online Data Supplements E and F.			
Clinical trials evaluating goal blood pressure reduction and optimal blood pressure-lowering agents in the setting of HFrEF and concomitant hypertension have not been done. However, it is apparent that in those patients at higher risk, blood pressure lowering is associated with fewer adverse cardiovascular events. GDMT for HFrEF with agents known to lower blood pressure should consider a goal blood pressure reduction consistent with a threshold now associated with improved clinical outcomes but not yet proven by RCTs in a population with HF.			

9.5.3. Treating Hypertension in Stage C HFpEF: Recommendation

Recommendation for Hypertension in Stage C HFpEF

COR	LOE	RECOMMENDATION	COMMENT/RATIONALE
I	C-LD	Patients with HFpEF and persistent hypertension after management of volume overload should be prescribed GDMT titrated to attain systolic blood pressure less than 130 mm Hg (9,167,169,170,195-199).	NEW: New target goal blood pressure based on updated interpretation of recent clinical trial data.
See Online Data Supplements E and F.			
The use of nitrates in the setting of HFpEF is associated with a signal of harm and, in most situations, should be avoided. For many common antihypertensive agents, including alpha blockers, beta blockers, and calcium channel blockers, there are limited data to guide the choice of antihypertensive therapy in the setting of HFpEF (172). Nevertheless, RAAS inhibition with ACE inhibitor, ARB (especially mineralocorticoid receptor antagonists), and possibly ARNI would represent the preferred choice. A shared decision-making discussion with the patient influenced by physician judgment should drive the ultimate choice of antihypertensive agents.			

9.6. Sleep-Disordered Breathing: Recommendations

(Moved from Section 7.3.1.4, Treatment of Sleep Disorders in the 2013 HF guideline.)

Recommendations for Treatment of Sleep Disorders

COR	LOE	RECOMMENDATIONS	COMMENT/RATIONALE
IIa See Online Data Supplement G.	C-LD	In patients with NYHA class II-IV HF and suspicion of sleep-disordered breathing or excessive daytime sleepiness, a formal sleep assessment is reasonable (200,201).	NEW: Recommendation reflects clinical necessity to distinguish obstructive versus central sleep apnea.
IIb See Online Data Supplement G.	B-R	In patients with cardiovascular disease and obstructive sleep apnea, CPAP may be reasonable to improve sleep quality and daytime sleepiness (204).	NEW: New data demonstrate the limited scope of benefit expected from CPAP for obstructive sleep apnea.
III: Harm See Online Data Supplement G.	B-R	In patients with NYHA class II-IV HFrEF and central sleep apnea, adaptive servo-ventilation causes harm (203).	NEW: New data demonstrate a signal of harm when adaptive servo-ventilation is used for central sleep apnea.

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 (202). It is clinically important to distinguish obstructive sleep apnea from central sleep apnea, given the different responses to treatment. Adaptive servo-ventilation for central sleep apnea is associated with harm (203). Continuous positive airway pressure (CPAP) for obstructive sleep apnea improves sleep quality, reduces the apnea-hypopnea index, and improves nocturnal oxygenation (200,201).

In patients with sleep apnea, a trial evaluated the impact of CPAP with usual therapy versus usual therapy alone on subsequent cardiovascular events, including HF (204). In this RCT of >2,700 patients, there was no evidence of benefit on cardiovascular events at a mean follow-up of 3.7 years for CPAP plus usual care compared with usual care alone. Improvements in sleep quality were noteworthy and represented the primary indication for initiating CPAP treatment (204). However, in patients with atrial fibrillation (AF) (a frequent comorbidity noted with HF), the use of CPAP for obstructive sleep apnea was helpful. In a trial of 10,132 patients with AF and obstructive sleep apnea, patients on CPAP treatment were less likely to progress to more permanent forms of AF than were patients without CPAP (205).

Mortality rate (all cause and cardiovascular) was higher with adaptive servo-ventilation plus GDMT than with GDMT alone in a single RCT to test the addition of adaptive servo-ventilation (≥ 5 hours/night, 7 days/week) to GDMT in patients with HFrEF and central sleep apnea (203). A similar risk has been seen in another trial, and a third trial of adaptive servo-ventilation in central sleep apnea and HF was aborted because of ethical concerns. The weight of evidence does not support the use of adaptive servo-ventilation for central sleep apnea in HFrEF.

PRESIDENTS AND STAFF

American College of Cardiology

Mary Norine Walsh, MD, FACC, President
Shalom Jacobovitz, Chief Executive Officer
William J. Oetgen, MD, MBA, FACC, Executive Vice President, Science, Education, Quality, and Publishing
Amelia Scholtz, PhD, Publications Manager, Science, Education, Quality, and Publishing
American College of Cardiology/American Heart Association
Katherine Sheehan, PhD, Director of Guideline Strategy and Operations
Lisa Bradfield, CAE, Director, Guideline Methodology and Policy

Abdul R. Abdullah, MD, Science and Medicine Advisor
Morgane Cibotti-Sun, MPH, Project Manager, Clinical Practice Guidelines
Sam Shahid, MBBS, MPH, Associate Science and Medicine Advisor
American Heart Association
Steven R. Houser, PhD, FAHA, President
Nancy Brown, Chief Executive Officer
Rose Marie Robertson, MD, FAHA, Chief Science and Medicine Officer
Gayle R. Whitman, PhD, RN, FAHA, FAAN, Senior Vice President, Office of Science Operations
Jody Hundley, Production Manager, Scientific Publications, Office of Science Operations

REFERENCES

- Committee on Standards for Developing Trustworthy Clinical Practice Guidelines, Institute of Medicine (U.S.). *Clinical Practice Guidelines We Can Trust*. Washington, DC: National Academies Press, 2011.
- Committee on Standards for Systematic Reviews of Comparative Effectiveness Research, Institute of Medicine (U.S.). *Finding What Works in Health Care: Standards for Systematic Reviews*. Washington, DC: National Academies Press, 2011.
- Anderson JL, Heidenreich PA, Barnett PG, et al. ACC/AHA statement on cost/value methodology in clinical practice guidelines and performance measures: a report of the American College of Cardiology/American Heart Association Task Force on Performance Measures and Task Force on Practice Guidelines. *J Am Coll Cardiol*. 2014;63:2304-22.
- ACCF/AHA Task Force on Practice Guidelines. *Methodology Manual and Policies From the ACCF/AHA Task Force on Practice Guidelines*. American College of Cardiology and American Heart Association, 2010. Available at: http://my.americanheart.org/idc/groups/ahamh-public/@wcm/@sop/documents/downloadable/ucm_319826.pdf. Accessed May 5, 2017.
- Halperin JL, Levine GN, Al-Khatib SM, et al. Further evolution of the ACC/AHA clinical practice guideline recommendation classification system: a report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines. *J Am Coll Cardiol*. 2016;67:1572-4.
- Jacobs AK, Kushner FG, Ettinger SM, et al. ACCF/AHA clinical practice guideline methodology submit report: a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines. *J Am Coll Cardiol*. 2013;61:213-65.
- Jacobs AK, Anderson JL, Halperin JL. The evolution and future of ACC/AHA clinical practice guidelines: a 30-year journey: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines. *J Am Coll Cardiol*. 2014;64:1373-84.
- Arnett DK, Goodman RA, Halperin JL, et al. AHA/ACC/HHS strategies to enhance application of clinical practice guidelines in patients with cardiovascular disease and comorbid conditions: from the American Heart Association, American College of Cardiology, and U.S. Department of Health and Human Services. *J Am Coll Cardiol*. 2014;64:1851-6.
- Yancy CW, Jessup M, Bozkurt B, et al. 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. *J Am Coll Cardiol*. 2013;62:e147-239.
- Yancy CW, Jessup M, Bozkurt B, et al. 2016 ACC/AHA/HFSA focused update on new pharmacological therapy for heart failure: an update of the 2013 ACCF/AHA guideline for the management of heart failure: a report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines and the Heart Failure Society of America. *J Am Coll Cardiol*. 2016;68:1476-88.
- Ponikowski P, Voors AA, Anker SD, et al. 2016 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure: The Task Force for the diagnosis and treatment of acute and chronic heart failure of the European Society of Cardiology (ESC). Developed with the special contribution of the Heart Failure Association (HFA) of the ESC. *Eur Heart J*. 2016;37:2129-200.
- Packer M, McMurray JJ, Desai AS, et al. Angiotensin receptor neprilysin inhibition compared with enalapril on the risk of clinical progression in surviving patients with heart failure. *Circulation*. 2015;131:54-61.
- Zile MR, Claggett BL, Prescott MF, et al. Prognostic Implications of Changes in N-Terminal Pro-B-Type Natriuretic Peptide in Patients With Heart Failure. *J Am Coll Cardiol*. 2016;68:2425-36.
- Solomon SD, Zile M, Pieske B, et al. The angiotensin receptor neprilysin inhibitor LCZ696 in heart failure with preserved ejection fraction: a phase 2 double-blind randomised controlled trial. *Lancet*. 2012;380:1387-95.
- Richards AM, Doughty R, Nicholls MG, et al. Plasma N-terminal pro-brain natriuretic peptide and adrenomedullin: prognostic utility and prediction of benefit from carvedilol in chronic ischemic left ventricular dysfunction. Australia-New Zealand Heart Failure Group. *J Am Coll Cardiol*. 2001;37:1781-7.
- Tang WH, Girod JP, Lee MJ, et al. Plasma B-type natriuretic peptide levels in ambulatory patients with established chronic symptomatic systolic heart failure. *Circulation*. 2003;108:2964-6.
- Zaphiriou A, Robb S, Murray-Thomas T, et al. The diagnostic accuracy of plasma BNP and NT-proBNP in patients referred from primary care with suspected heart failure: results of the UK natriuretic peptide study. *Eur J Heart Fail*. 2005;7:537-41.
- Son CS, Kim YN, Kim HS, et al. Decision-making model for early diagnosis of congestive heart failure using rough set and decision tree approaches. *J Biomed Inform*. 2012;45:999-1008.
- Kelder JC, Cramer MJ, Van WJ, et al. The diagnostic value of physical examination and additional testing in primary care patients with suspected heart failure. *Circulation*. 2011;124:2865-73.
- Balton C, Don-Wauchope A, Hill S, et al. Use of Natriuretic Peptide Measurement in the Management of Heart Failure [Internet]. 13(14)-EHC118-EF ed. Rockville, MD: 2013.
- Booth RA, Hill SA, Don-Wauchope A, et al. Performance of BNP and NT-proBNP for diagnosis of heart failure in primary care patients: a systematic review. *Heart Fail Rev*. 2014;19:439-51.
- Dao Q, Krishnaswamy P, Kazanegra R, et al. Utility of B-type natriuretic peptide in the diagnosis of congestive heart failure in an urgent-care setting. *J Am Coll Cardiol*. 2001;37:379-85.
- Davis M, Espiner E, Richards G, et al. Plasma brain natriuretic peptide in assessment of acute dyspnea. *Lancet*. 1994;343:440-4.
- Maisel AS, Krishnaswamy P, Nowak RM, et al. Rapid measurement of B-type natriuretic peptide in the emergency diagnosis of heart failure. *N Engl J Med*. 2002;347:161-7.
- Moe GW, Howlett J, Januzzi JL, et al. N-terminal pro-B-type natriuretic peptide testing improves the management of patients with suspected acute heart failure: primary results of the Canadian prospective randomized multicenter IMPROVE-CHF study. *Circulation*. 2007;115:3103-10.
- Mueller C, Scholer A, Laule-Kilian K, et al. Use of B-type natriuretic peptide in the evaluation and management of acute dyspnea. *N Engl J Med*. 2004;350:647-54.
- van Kimmenade RR, Pinto YM, Bayes-Genis A, et al. Usefulness of intermediate amino-terminal pro-brain natriuretic peptide concentrations for diagnosis and prognosis of acute heart failure. *Am J Cardiol*. 2006;98:386-90.
- Januzzi JL Jr, Chen-Tournoux AA, Moe G. Amino-terminal pro-B-type natriuretic peptide testing for the diagnosis or exclusion of heart failure in patients with acute symptoms. *Am J Cardiol*. 2008;101:29-38.
- Santaguida PL, Don-Wauchope AC, Ali U, et al. Incremental value of natriuretic peptide measurement in acute decompensated heart failure (ADHF): a systematic review. *Heart Fail Rev*. 2014;19:507-19.
- Hill SA, Booth RA, Santaguida PL, et al. Use of BNP and NT-proBNP for the diagnosis of heart failure in the emergency department: a systematic review of the evidence. *Heart Fail Rev*. 2014;19:421-38.
- Costello-Boerrigter LC, Boerrigter G, Redfield MM, et al. Amino-terminal pro-B-type natriuretic peptide and B-type natriuretic peptide in the general community: determinants and detection of left ventricular dysfunction. *J Am Coll Cardiol*. 2006;47:345-53.
- de Lemos JA, McGuire DK, Khera A, et al. Screening the population for left ventricular hypertrophy and left ventricular systolic dysfunction using natriuretic peptides: results from the Dallas Heart Study. *Am Heart J*. 2009;157:746-53.
- Goetze JP, Mogelvang R, Maage L, et al. Plasma pro-B-type natriuretic peptide in the general population: screening for left ventricular hypertrophy and systolic dysfunction. *Eur Heart J*. 2006;27:3004-10.
- Ng LL, Loke IW, Davies JE, et al. Community screening for left ventricular systolic dysfunction using plasma and urinary natriuretic peptides. *J Am Coll Cardiol*. 2005;45:1043-50.
- Ho JE, Liu C, Lyass A, et al. Galectin-3, a marker of cardiac fibrosis, predicts incident heart failure in the community. *J Am Coll Cardiol*. 2012;60:1249-56.
- Wang TJ, Wollert KC, Larson MG, et al. Prognostic utility of novel biomarkers of cardiovascular stress: the Framingham Heart Study. *Circulation*. 2012;126:1596-604.
- Xanthakis V, Larson MG, Wollert KC, et al. Association of novel biomarkers of cardiovascular stress with left ventricular hypertrophy and dysfunction: implications for screening. *J Am Heart Assoc*. 2013;2:e000399.
- Anwaruddin S, Lloyd-Jones DM, Baggish A, et al. Renal function, congestive heart failure, and amino-terminal pro-brain natriuretic peptide measurement: results from the ProBNP Investigation of Dyspnea in the Emergency Department (PRIDE) Study. *J Am Coll Cardiol*. 2006;47:91-7.
- Redfield MM, Rodeheffer RJ, Jacobsen SJ, et al. Plasma brain natriuretic peptide concentration: impact of age and gender. *J Am Coll Cardiol*. 2002;40:976-82.

40. Wang TJ, Larson MG, Levy D, et al. Impact of age and sex on plasma natriuretic peptide levels in healthy adults. *Am J Cardiol*. 2002;90:254-8.
41. Chang AY, Abdullah SM, Jain T, et al. Associations among androgens, estrogens, and natriuretic peptides in young women: observations from the Dallas Heart Study. *J Am Coll Cardiol*. 2007;49:109-16.
42. Clerico A, Giannoni A, Vittorini S, et al. The paradox of low BNP levels in obesity. *Heart Fail Rev*. 2012;17:81-96.
43. De Vecchis R, Esposito C, Di Biase G, et al. B-type natriuretic peptide-guided versus symptom-guided therapy in outpatients with chronic heart failure: a systematic review with meta-analysis. *J Cardiovasc Med (Hagerstown)*. 2014;15:122-34.
44. Felker GM, Hasselblad V, Hernandez AF, et al. Biomarker-guided therapy in chronic heart failure: a meta-analysis of randomized controlled trials. *Am Heart J*. 2009;158:422-30.
45. Li P, Luo Y, Chen YM. B-type natriuretic peptide-guided chronic heart failure therapy: a meta-analysis of 11 randomised controlled trials. *Heart Lung Circ*. 2013;22:852-60.
46. Porapakkham P, Porapakkham P, Zimmet H, et al. B-type natriuretic peptide-guided heart failure therapy: a meta-analysis. *Arch Intern Med*. 2010;170:507-14.
47. Savarese G, Trimarco B, Dellegrottaglie S, et al. Natriuretic peptide-guided therapy in chronic heart failure: a meta-analysis of 2,686 patients in 12 randomized trials. *PLoS One*. 2013;8:e58287.
48. Troughton RW, Frampton CM, Brunner-La Rocca HP, et al. Effect of B-type natriuretic peptide-guided treatment of chronic heart failure on total mortality and hospitalization: an individual patient meta-analysis. *Eur Heart J*. 2014;35:1559-67.
49. Xin W, Lin Z, Mi S. Does B-type natriuretic peptide-guided therapy improve outcomes in patients with chronic heart failure? A systematic review and meta-analysis of randomized controlled trials. *Heart Fail Rev*. 2015;20:69-80.
50. Berger R, Moertl D, Peter S, et al. N-terminal pro-B-type natriuretic peptide-guided, intensive patient management in addition to multidisciplinary care in chronic heart failure: a 3-arm, prospective, randomized pilot study. *J Am Coll Cardiol*. 2010;55:645-53.
51. Eurlings LW, van Poel PE, Kok WE, et al. Management of chronic heart failure guided by individual N-terminal pro-B-type natriuretic peptide targets: results of the PRIMA (Can Pro-brain-natriuretic peptide guided therapy of chronic heart failure improve heart failure morbidity and mortality?) study. *J Am Coll Cardiol*. 2010;56:2090-100.
52. Gaggin HK, Mohammed AA, Bhardwaj A, et al. Heart failure outcomes and benefits of NT-proBNP-guided management in the elderly: results from the prospective, randomized ProBNP outpatient tailored chronic heart failure therapy (PROTECT) study. *J Card Fail*. 2012;18:626-34.
53. Jourdain P, Jondeau G, Funck F, et al. Plasma brain natriuretic peptide-guided therapy to improve outcome in heart failure: the STARS-BNP Multicenter Study. *J Am Coll Cardiol*. 2007;49:1733-9.
54. Karlstrom P, Alehagen U, Boman K, et al. Brain natriuretic peptide-guided treatment does not improve morbidity and mortality in extensively treated patients with chronic heart failure: responders to treatment have a significantly better outcome. *Eur J Heart Fail*. 2011;13:1096-103.
55. Lainchbury JG, Troughton RW, Strangman KM, et al. N-terminal pro-B-type natriuretic peptide-guided treatment for chronic heart failure: results from the BATTLESCARRED (NT-proBNP-Assisted Treatment To Lessen Serial Cardiac Readmissions and Death) trial. *J Am Coll Cardiol*. 2009;55:53-60.
56. Persson H, Erntell H, Eriksson B, et al. Improved pharmacological therapy of chronic heart failure in primary care: a randomized study of NT-proBNP Guided Management of Heart Failure-SIGNAL-HF (Swedish Intervention study-Guidelines and NT-proBNP Analysis in Heart Failure). *Eur J Heart Fail*. 2010;12:1300-8.
57. Pfisterer M, Buser P, Rickli H, et al. BNP-guided vs symptom-guided heart failure therapy: the Trial of Intensified vs Standard Medical Therapy in Elderly Patients With Congestive Heart Failure (TIME-CHF) randomized trial. *JAMA*. 2009;301:383-92.
58. Shah MR, Califf RM, Nohria A, et al. The STARBRIT trial: a randomized, pilot study of B-type natriuretic peptide-guided therapy in patients with advanced heart failure. *J Card Fail*. 2011;17:613-21.
59. Troughton RW, Frampton CM, Yandle TG, et al. Treatment of heart failure guided by plasma amino-terminal brain natriuretic peptide (N-BNP) concentrations. *Lancet*. 2000;355:1126-30.
60. Singer AJ, Birkhahn RH, Guss D, et al. Rapid Emergency Department Heart Failure Outpatients Trial (REDHOT II): a randomized controlled trial of the effect of serial B-type natriuretic peptide testing on patient management. *Circ Heart Fail*. 2009;2:287-93.
61. Stienen S, Salah K, Moons AH, et al. Rationale and design of PRIMA II: A multicenter, randomized clinical trial to study the impact of in-hospital guidance for acute decompensated heart failure treatment by a predefined NT-ProBNP target on the reduction of readmission and Mortality rates. *Am Heart J*. 2014;168:30-6.
62. Stienen S. PRIMA II: can NT-pro-brain-natriuretic peptide (NT-proBNP) guided therapy during admission for acute heart failure reduce mortality and readmissions? *J Card Fail*. 2016;22:939-40.
63. Kociol RD, Pang PS, Gheorghiade M, et al. Troponin elevation in heart failure prevalence, mechanisms, and clinical implications. *J Am Coll Cardiol*. 2010;56:1071-8.
64. Amsterdam EA, Wenger NK, Brindis RG, et al. 2014 AHA/ACC guideline for the management of patients with non-ST-elevation acute coronary syndromes: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines. *J Am Coll Cardiol*. 2014;64:e139-228.
65. Masson S, Anand I, Favero C, et al. Serial measurement of cardiac troponin T using a highly sensitive assay in patients with chronic heart failure: data from 2 large randomized clinical trials. *Circulation*. 2012;125:280-8.
66. Savarese G, Musella F, D'Amore C, et al. Changes of natriuretic peptides predict hospital admissions in patients with chronic heart failure: a meta-analysis. *J Am Coll Cardiol HF*. 2014;2:148-58.
67. de Lemos JA. Increasingly sensitive assays for cardiac troponins: a review. *JAMA*. 2013;309:2262-9.
68. de Boer RA, Daniels LB, Maisel AS, et al. State of the Art: Newer biomarkers in heart failure. *Eur J Heart Fail*. 2015;17:559-69.
69. Gopal DM, Sam F. New and emerging biomarkers in left ventricular systolic dysfunction-insight into dilated cardiomyopathy. *J Cardiovasc Transl Res*. 2013;6:516-27.
70. O'Meara E, de DS, Rouleau JL, et al. Circulating biomarkers in patients with heart failure and preserved ejection fraction. *Curr Heart Fail Rep*. 2013;10:350-8.
71. Karayannis G, Triposkiadis F, Skoularigis J, et al. The emerging role of Galectin-3 and ST2 in heart failure: practical considerations and pitfalls using novel biomarkers. *Curr Heart Fail Rep*. 2013;10:441-9.
72. Ahmad T, Fuzat M, Neely B, et al. Biomarkers of myocardial stress and fibrosis as predictors of mode of death in patients with chronic heart failure. *J Am Coll Cardiol HF*. 2014;2:260-8.
73. Bayes-Genis A, de AM, Vila J, et al. Head-to-head comparison of 2 myocardial fibrosis biomarkers for long-term heart failure risk stratification: ST2 versus galectin-3. *J Am Coll Cardiol*. 2014;63:158-66.
74. Gaggin HK, Szymonifka J, Bhardwaj A, et al. Head-to-head comparison of serial soluble ST2, growth differentiation factor-15, and highly-sensitive troponin T measurements in patients with chronic heart failure. *J Am Coll Cardiol HF*. 2014;2:65-72.
75. Ky B, French B, Levy WC, et al. Multiple biomarkers for risk prediction in chronic heart failure. *Circ Heart Fail*. 2012;5:183-90.
76. Sabatine MS, Morrow DA, de Lemos JA, et al. Evaluation of multiple biomarkers of cardiovascular stress for risk prediction and guiding medical therapy in patients with stable coronary disease. *Circulation*. 2012;125:233-40.
77. Ahmad T, Fuzat M, Pencina MJ, et al. Charting a roadmap for heart failure biomarker studies. *J Am Coll Cardiol HF*. 2014;2:477-88.
78. Miller WL, Hartman KA, Grill DE, et al. Serial measurements of midregion proANP and copeptin in ambulatory patients with heart failure: incremental prognostic value of novel biomarkers in heart failure. *Heart*. 2012;98:389-94.
79. Creemers EE, Tijssen AJ, Pinto YM. Circulating microRNAs: novel biomarkers and extracellular communicators in cardiovascular disease? *Circ Res*. 2012;110:483-95.
80. Wong LL, Armugam A, Sepramaniam S, et al. Circulating microRNAs in heart failure with reduced and preserved left ventricular ejection fraction. *Eur J Heart Fail*. 2015;17:393-404.
81. Ovchinnikova ES, Schmitter D, Vegter EL, et al. Signature of circulating microRNAs in patients with acute heart failure. *Eur J Heart Fail*. 2016;18:414-23.
82. Shah SH, Kraus WE, Newgard CB. Metabolomic profiling for the identification of novel biomarkers and mechanisms related to common cardiovascular diseases: form and function. *Circulation*. 2012;126:1110-20.
83. Cheng ML, Wang CH, Shiao MS, et al. Metabolic disturbances identified in plasma are associated with outcomes in patients with heart failure: diagnostic and prognostic value of metabolomics. *J Am Coll Cardiol*. 2015;65:1509-20.

84. Zheng Y, Yu B, Alexander D, et al. Associations between metabolomic compounds and incident heart failure among African Americans: the ARIC Study. *Am J Epidemiol*. 2013;178:534-42.
85. Ledwidge M, Gallagher J, Conlon C, et al. Natriuretic peptide-based screening and collaborative care for heart failure: the STOP-HF randomized trial. *JAMA*. 2013;310:66-74.
86. Huelsmann M, Neuhold S, Resl M, et al. PONTIAC (NT-proBNP selected prevention of cardiac events in a population of diabetic patients without a history of cardiac disease): a prospective randomized controlled trial. *J Am Coll Cardiol*. 2013;62:1365-72.
87. Anand IS, Fisher LD, Chiang YT, et al. Changes in brain natriuretic peptide and norepinephrine over time and mortality and morbidity in the Valsartan Heart Failure Trial (Val-HeFT). *Circulation*. 2003;107:1278-83.
88. Berger R, Huelsman M, Strecker K, et al. B-type natriuretic peptide predicts sudden death in patients with chronic heart failure. *Circulation*. 2002;105:2392-7.
89. Forfia PR, Watkins SP, Rame JE, et al. Relationship between B-type natriuretic peptides and pulmonary capillary wedge pressure in the intensive care unit. *J Am Coll Cardiol*. 2005;45:1667-71.
90. Maeda K, Tsutamoto T, Wada A, et al. High levels of plasma brain natriuretic peptide and interleukin-6 after optimized treatment for heart failure are independent risk factors for morbidity and mortality in patients with congestive heart failure. *J Am Coll Cardiol*. 2000;36:1587-93.
91. Neuhold S, Huelsmann M, Strunk G, et al. Comparison of copeptin, B-type natriuretic peptide, and amino-terminal pro-B-type natriuretic peptide in patients with chronic heart failure: prediction of death at different stages of the disease. *J Am Coll Cardiol*. 2008;52:266-72.
92. Taub PR, Daniels LB, Maisel AS. Usefulness of B-type natriuretic peptide levels in predicting hemodynamic and clinical decompensation. *Heart Fail Clin*. 2009;5:169-75.
93. Bettencourt P, Azevedo A, Pimenta J, et al. N-terminal-pro-brain natriuretic peptide predicts outcome after hospital discharge in heart failure patients. *Circulation*. 2004;110:2168-74.
94. Cheng V, Kazanagra R, Garcia A, et al. A rapid bedside test for B-type peptide predicts treatment outcomes in patients admitted for decompensated heart failure: a pilot study. *J Am Coll Cardiol*. 2001;37:386-91.
95. Fonarow GC, Peacock WF, Horwich TB, et al. Usefulness of B-type natriuretic peptide and cardiac troponin levels to predict in-hospital mortality from ADHERE. *Am J Cardiol*. 2008;101:231-7.
96. Logeart D, Thabut G, Jourdain P, et al. Pre-discharge B-type natriuretic peptide assay for identifying patients at high risk of re-admission after decompensated heart failure. *J Am Coll Cardiol*. 2004;43:635-41.
97. Maisel A, Hollander JE, Guss D, et al. Primary results of the Rapid Emergency Department Heart Failure Outpatient Trial (REDHOT). A multicenter study of B-type natriuretic peptide levels, emergency department decision making, and outcomes in patients presenting with shortness of breath. *J Am Coll Cardiol*. 2004;44:1328-33.
98. Zairis MN, Tsiaousis GZ, Georgilas AT, et al. Multitasker strategy for the prediction of 31 days cardiac death in patients with acutely decompensated chronic heart failure. *Int J Cardiol*. 2010;141:284-90.
99. Peacock WFI, De Marco T, Fonarow GC, et al. Cardiac troponin and outcome in acute heart failure. *N Engl J Med*. 2008;358:2117-26.
100. Lee DS, Stitt A, Austin PC, et al. Prediction of heart failure mortality in emergent care: a cohort study. *Ann Intern Med*. 2012;156:767-75.
101. Santaguida PL, Don-Wauchope AC, Oremus M, et al. BNP and NT-proBNP as prognostic markers in persons with acute decompensated heart failure: a systematic review. *Heart Fail Rev*. 2014;19:453-70.
102. Horwich TB, Patel J, MacLellan WR, et al. Cardiac troponin I is associated with impaired hemodynamics, progressive left ventricular dysfunction, and increased mortality rates in advanced heart failure. *Circulation*. 2003;108:833-8.
103. Ilva T, Lassus J, Siirila-Waris K, et al. Clinical significance of cardiac troponins I and T in acute heart failure. *Eur J Heart Fail*. 2008;10:772-9.
104. Dhalwal AS, Deswal A, Pritchett A, et al. Reduction in BNP levels with treatment of decompensated heart failure and future clinical events. *J Card Fail*. 2009;15:293-9.
105. O'Connor CM, Hasselblad V, Mehta RH, et al. Triage after hospitalization with advanced heart failure: the ESCAPE (Evaluation Study of Congestive Heart Failure and Pulmonary Artery Catheterization Effectiveness) risk model and discharge score. *J Am Coll Cardiol*. 2010;55:872-8.
106. O'Brien RJ, Squire IB, Demme B, et al. Pre-discharge, but not admission, levels of NT-proBNP predict adverse prognosis following acute LVF. *Eur J Heart Fail*. 2003;5:499-506.
107. Cohen-Solal A, Logeart D, Huang B, et al. Lowered B-type natriuretic peptide in response to levosimendan or dobutamine treatment is associated with improved survival in patients with severe acutely decompensated heart failure. *J Am Coll Cardiol*. 2009;53:2343-8.
108. Salah K, Kok WE, Eurlings LW, et al. A novel discharge risk model for patients hospitalised for acute decompensated heart failure incorporating N-terminal pro-B-type natriuretic peptide levels: a European coLLaboration on Acute decompensated Heart Failure: ELAN-HF Score. *Heart*. 2014;100:115-25.
109. Flint KM, Allen LA, Pham M, et al. B-type natriuretic peptide predicts 30-day readmission for heart failure but not readmission for other causes. *J Am Heart Assoc*. 2014;3:e000806.
110. Kociol RD, Horton JR, Fonarow GC, et al. Admission, discharge, or change in B-type natriuretic peptide and long-term outcomes: data from Organized Program to Initiate Lifesaving Treatment in Hospitalized Patients with Heart Failure (OPTIMIZE-HF) linked to Medicare claims. *Circ Heart Fail*. 2011;4:628-36.
111. Kociol RD, McNulty SE, Hernandez AF, et al. Markers of decongestion, dyspnea relief, and clinical outcomes among patients hospitalized with acute heart failure. *Circ Heart Fail*. 2013;6:240-5.
112. Verdiani V, Ognibene A, Rutili MS, et al. NT-ProBNP reduction percentage during hospital stay predicts long-term mortality and readmission in heart failure patients. *J Cardiovasc Med (Hagerstown)*. 2008;9:694-9.
113. Bayes-Genis A, Lopez L, Zapico E, et al. NT-ProBNP reduction percentage during admission for acutely decompensated heart failure predicts long-term cardiovascular mortality. *J Card Fail*. 2005;11:53-8.
114. Alonso-Martinez JL, Llorente-Diez B, Echegaray-Agata M, et al. C-reactive protein as a predictor of improvement and readmission in heart failure. *Eur J Heart Fail*. 2002;4:331-6.
115. Dieplinger B, Gegenhuber A, Kaar G, et al. Prognostic value of established and novel biomarkers in patients with shortness of breath attending an emergency department. *Clin Biochem*. 2010;43:714-9.
116. Januzzi JL Jr, Peacock WF, Maisel AS, et al. Measurement of the interleukin family member ST2 in patients with acute dyspnea: results from the PRIDE (Pro-Brain Natriuretic Peptide Investigation of Dyspnea in the Emergency Department) study. *J Am Coll Cardiol*. 2007;50:607-13.
117. Manzano-Fernandez S, Mueller T, Pascual-Figal D, et al. Usefulness of soluble concentrations of interleukin family member ST2 as predictor of mortality in patients with acutely decompensated heart failure relative to left ventricular ejection fraction. *Am J Cardiol*. 2011;107:259-67.
118. Rehman SU, Mueller T, Januzzi JL Jr. Characteristics of the novel interleukin family biomarker ST2 in patients with acute heart failure. *J Am Coll Cardiol*. 2008;52:1458-65.
119. Shah RV, Chen-Tournoux AA, Picard MH, et al. Galectin-3, cardiac structure and function, and long-term mortality in patients with acutely decompensated heart failure. *Eur J Heart Fail*. 2010;12:826-32.
120. de Boer RA, Lok DJ, Jaarsma T, et al. Predictive value of plasma galectin-3 levels in heart failure with reduced and preserved ejection fraction. *Ann Med*. 2011;43:60-8.
121. Lok DJ, van der Meer P, de la Porte PW, et al. Prognostic value of galectin-3, a novel marker of fibrosis, in patients with chronic heart failure: data from the DEAL-HF study. *Clin Res Cardiol*. 2010;99:323-8.
122. Tang WH, Shrestha K, Shao Z, et al. Usefulness of plasma galectin-3 levels in systolic heart failure to predict renal insufficiency and survival. *Am J Cardiol*. 2011;108:385-90.
123. Tang WH, Wu Y, Grodin JL, et al. Prognostic Value of Baseline and Changes in Circulating Soluble ST2 Levels and the Effects of Nesiritide in Acute Decompensated Heart Failure. *J Am Coll Cardiol HF*. 2016;4:68-77.
124. Januzzi JL, Mebazaa A, Di SS. ST2 and prognosis in acutely decompensated heart failure: the International ST2 Consensus Panel. *Am J Cardiol*. 2015;115:26B-31B.
125. Mebazaa A, Di SS, Maisel AS, et al. ST2 and multitasker testing in acute decompensated heart failure. *Am J Cardiol*. 2015;115:38B-43B.
126. Ferrmann GJ, Lindsell CJ, Storrow AB, et al. Galectin 3 complements BNP in risk stratification in acute heart failure. *Biomarkers*. 2012;17:706-13.
127. Lassus J, Gayat E, Mueller C, et al. Incremental value of biomarkers to clinical variables for mortality

prediction in acutely decompensated heart failure: the Multinational Observational Cohort on Acute Heart Failure (MOCA) study. *Int J Cardiol*. 2013;168:2186-94.

128. Effects of enalapril on mortality in severe congestive heart failure. Results of the Cooperative North Scandinavian Enalapril Survival Study (CONSENSUS). The CONSENSUS Trial Study Group. *N Engl J Med*. 1987;316:1429-35.

129. Effect of enalapril on survival in patients with reduced left ventricular ejection fractions and congestive heart failure. The SOLVD Investigators. *N Engl J Med*. 1991;325:293-302.

130. Packer M, Poole-Wilson PA, Armstrong PW, et al. Comparative effects of low and high doses of the angiotensin-converting enzyme inhibitor, lisinopril, on morbidity and mortality in chronic heart failure. ATLAS Study Group. *Circulation*. 1999;100:2312-8.

131. Pfeffer MA, Braunwald E, Moyé LA, et al. Effect of captopril on mortality and morbidity in patients with left ventricular dysfunction after myocardial infarction: results of the Survival and Ventricular Enlargement Trial. The SAVE Investigators. *N Engl J Med*. 1992;327:669-77.

132. Effect of ramipril on mortality and morbidity of survivors of acute myocardial infarction with clinical evidence of heart failure. The Acute Infarction Ramipril Efficacy (AIRE) Study Investigators. *Lancet*. 1993;342:821-8.

133. Kober L, Torp-Pedersen C, Carlsen JE, et al. A clinical trial of the angiotensin-converting-enzyme inhibitor trandolapril in patients with left ventricular dysfunction after myocardial infarction. Trandolapril Cardiac Evaluation (TRACE) Study Group. *N Engl J Med*. 1995;333:1670-6.

134. Cohn JN, Tognoni G, Investigators VHFT. A randomized trial of the angiotensin-receptor blocker valsartan in chronic heart failure. *N Engl J Med*. 2001;345:1667-75.

135. Pfeffer MA, McMurray JJV, Velazquez EJ, et al. Valsartan, captopril, or both in myocardial infarction complicated by heart failure, left ventricular dysfunction, or both. *N Engl J Med*. 2003;349:1893-906.

136. Konstam MA, Neaton JD, Dickstein K, et al. Effects of high-dose versus low-dose losartan on clinical outcomes in patients with heart failure (HEAAL study): a randomised, double-blind trial. *Lancet*. 2009;374:1840-8.

137. Pfeffer MA, Swedberg K, Granger CB, et al. Effects of candesartan on mortality and morbidity in patients with chronic heart failure: the CHARM-Overall programme. *Lancet*. 2003;362:759-66.

138. McMurray JJV, Packer M, Desai AS, et al. Angiotensin-neprilysin inhibition versus enalapril in heart failure. *N Engl J Med*. 2014;371:993-1004.

139. Effect of metoprolol CR/XL in chronic heart failure: Metoprolol CR/XL Randomised Intervention Trial in Congestive Heart Failure (MERIT-HF). *Lancet*. 1999;353:2001-7.

140. Packer M, Fowler MB, Roecker EB, et al. Effect of carvedilol on the morbidity of patients with severe chronic heart failure: results of the carvedilol prospective randomized cumulative survival (COPERNICUS) study. *Circulation*. 2002;106:2194-9.

141. Eschaler R, McMurray JJV, Swedberg K, et al. Safety and efficacy of eplerenone in patients at high risk for hyperkalemia and/or worsening renal function:

analyses of the EMPHASIS-HF study subgroups (Eplerenone in Mild Patients Hospitalization And Survival Study in Heart Failure). *J Am Coll Cardiol*. 2013;62:1585-93.

142. Pitt B, Zannad F, Remme WJ, et al. The effect of spironolactone on morbidity and mortality in patients with severe heart failure. Randomized Aldactone Evaluation Study Investigators. *N Engl J Med*. 1999;341:709-17.

143. Garg R, Yusuf S. Overview of randomized trials of angiotensin-converting enzyme inhibitors on mortality and morbidity in patients with heart failure. Collaborative Group on ACE Inhibitor Trials. *JAMA*. 1995;273:1450-6.

144. Woodard-Grice AV, Lucisano AC, Byrd JB, et al. Sex-dependent and race-dependent association of XPNPEP2 C-2399A polymorphism with angiotensin-converting enzyme inhibitor-associated angioedema. *Pharmacogenet Genomics*. 2010;20:532-6.

145. Yusuf S, Teo KK, Pogue J, et al. Telmisartan, ramipril, or both in patients at high risk for vascular events. *N Engl J Med*. 2008;358:1547-59.

146. Yusuf S, Teo K, Anderson C, et al. Effects of the angiotensin-receptor blocker telmisartan on cardiovascular events in high-risk patients intolerant to angiotensin-converting enzyme inhibitors: a randomised controlled trial. *Lancet*. 2008;372:1174-83.

147. Entresto [package insert]. Hanover, NJ: Novartis Pharmaceuticals Corporation, 2015.

148. Packer M, Califf RM, Konstam MA, et al. Comparison of omapatrilat and enalapril in patients with chronic heart failure: the Omapatrilat Versus Enalapril Randomized Trial of Utility in Reducing Events (OVERTURE). *Circulation*. 2002;106:920-6.

149. Kostis JB, Packer M, Black HR, et al. Omapatrilat and enalapril in patients with hypertension: the Omapatrilat Cardiovascular Treatment vs. Enalapril (OCTAVE) trial. *Am J Hypertens*. 2004;17:103-11.

150. Vardeny O, Miller R, Solomon SD. Combined neprilysin and renin-angiotensin system inhibition for the treatment of heart failure. *J Am Coll Cardiol HF*. 2014;2:663-70.

151. Messerli FH, Nussberger J. Vasopeptidase inhibition and angio-oedema. *Lancet*. 2000;356:608-9.

152. Braunwald E. The path to an angiotensin receptor antagonist-neprilysin inhibitor in the treatment of heart failure. *J Am Coll Cardiol*. 2015;65:1029-41.

153. Ruilope LM, Dukar A, Böhm M, et al. Blood-pressure reduction with LCZ696, a novel dual-acting inhibitor of the angiotensin II receptor and neprilysin: a randomised, double-blind, placebo-controlled, active comparator study. *Lancet*. 2010;375:1255-66.

154. Böhm M, Robertson M, Ford I, et al. Influence of cardiovascular and noncardiovascular co-morbidities on outcomes and treatment effect of heart rate reduction with ivabradine in stable heart failure (from the SHIFT Trial). *Am J Cardiol*. 2015;116:1890-7.

155. Swedberg K, Komajda M, Böhm M, et al. Ivabradine and outcomes in chronic heart failure (SHIFT): a randomised placebo-controlled study. *Lancet*. 2010;376:875-85.

156. Fox K, Ford I, Steg PG, et al. Ivabradine in stable coronary artery disease without clinical heart failure. *N Engl J Med*. 2014;371:1091-9.

157. Fox K, Ford I, Steg PG, et al. Ivabradine for patients with stable coronary artery disease and left-ventricular systolic dysfunction (BEAUTIFUL): a randomised, double-blind, placebo-controlled trial. *Lancet*. 2008;372:807-16.

158. Pitt B, Segal R, Martinez FA, et al. Randomised trial of losartan versus captopril in patients over 65 with heart failure (Evaluation of Losartan in the Elderly Study, ELITE). *Lancet*. 1997;349:747-52.

159. Pitt B, Remme W, Zannad F, et al. Eplerenone, a selective aldosterone blocker, in patients with left ventricular dysfunction after myocardial infarction. *N Engl J Med*. 2003;348:1309-21.

160. Authors CI. The Cardiac Insufficiency Bisoprolol Study II (CIBIS-II): a randomised trial. *Lancet*. 1999;353:9-13.

161. Packer M, Coats AJ, Fowler MB, et al. Effect of carvedilol on survival in severe chronic heart failure. *N Engl J Med*. 2001;344:1651-8.

162. Taylor AL, Ziesche S, Yancy C, et al. Combination of isosorbide dinitrate and hydralazine in blacks with heart failure. *N Engl J Med*. 2004;351:2049-57.

163. Cohn JN, Archibald DG, Ziesche S, et al. Effect of vasodilator therapy on mortality in chronic congestive heart failure. Results of a Veterans Administration Cooperative Study. *N Engl J Med*. 1986;314:1547-52.

164. Chobanian AV, Bakris GL, Black HR, et al. Seventh report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure. *Hypertension*. 2003;42:1206-52.

165. Levy D, Larson MG, Vasan RS, et al. The progression from hypertension to congestive heart failure. *JAMA*. 1996;275:1557-62.

166. Pitt B, Pfeffer MA, Assmann SF, et al. Spironolactone for heart failure with preserved ejection fraction. *N Engl J Med*. 2014;370:1383-92.

167. Pfeffer MA, Claggett B, Assmann SF, et al. Regional variation in patients and outcomes in the Treatment of Preserved Cardiac Function Heart Failure With an Aldosterone Antagonist (TOPCAT) trial. *Circulation*. 2015;131:34-42.

168. Edelmann F, Wachter R, Schmidt AG, et al. Effect of spironolactone on diastolic function and exercise capacity in patients with heart failure with preserved ejection fraction: the Aldo-DHF randomized controlled trial. *JAMA*. 2013;309:781-91.

169. Yusuf S, Pfeffer MA, Swedberg K, et al. Effects of candesartan in patients with chronic heart failure and preserved left-ventricular ejection fraction: the CHARM-Preserved Trial. *Lancet*. 2003;362:777-81.

170. Massie BM, Carson PE, McMurray JJ, et al. Irbesartan in patients with heart failure and preserved ejection fraction. *N Engl J Med*. 2008;359:2456-67.

171. Redfield MM, Anstrom KJ, Levine JA, et al. Isosorbide Mononitrate in Heart Failure with Preserved Ejection Fraction. *N Engl J Med*. 2015;373:2314-24.

172. Redfield MM, Chen HH, Borlaug BA, et al. Effect of phosphodiesterase-5 inhibition on exercise capacity and clinical status in heart failure with preserved ejection fraction: a randomized clinical trial. *JAMA*. 2013;309:1268-77.

173. Anker SD, Comin CJ, Filippatos G, et al. Ferric carboxymaltose in patients with heart failure and iron deficiency. *N Engl J Med*. 2009;361:2436-48.

174. Ponikowski P, van Veldhuisen DJ, Comin-Colet J, et al. Beneficial effects of long-term intravenous iron therapy with ferric carboxymaltose in patients with symptomatic heart failure and iron deficiency. *Eur Heart J*. 2015;36:657-68.
175. Kapoor M, Schleinitz MD, Gemignani A, et al. Outcomes of patients with chronic heart failure and iron deficiency treated with intravenous iron: a meta-analysis. *Cardiovasc Hematol Disord Drug Targets*. 2013;13:35-44.
176. Swedberg K, Young JB, Anand IS, et al. Treatment of anemia with darbepoetin alfa in systolic heart failure. *N Engl J Med*. 2013;368:1210-9.
177. Cleland JG, Sullivan JT, Ball S, et al. Once-monthly administration of darbepoetin alfa for the treatment of patients with chronic heart failure and anemia: a pharmacokinetic and pharmacodynamic investigation. *J Cardiovasc Pharmacol*. 2005;46:155-61.
178. Klapholz M, Abraham WT, Ghali JK, et al. The safety and tolerability of darbepoetin alfa in patients with anaemia and symptomatic heart failure. *Eur J Heart Fail*. 2009;11:1071-7.
179. Ponikowski P, Anker SD, Szachniewicz J, et al. Effect of darbepoetin alfa on exercise tolerance in anemic patients with symptomatic chronic heart failure: a randomized, double-blind, placebo-controlled trial. *J Am Coll Cardiol*. 2007;49:753-62.
180. Silverberg DS, Wexler D, Sheps D, et al. The effect of correction of mild anemia in severe, resistant congestive heart failure using subcutaneous erythropoietin and intravenous iron: a randomized controlled study. *J Am Coll Cardiol*. 2001;37:1775-80.
181. van der Meer P, Groenveld HF, Januzzi JL Jr, et al. Erythropoietin treatment in patients with chronic heart failure: a meta-analysis. *Heart*. 2009;95:1309-14.
182. van Veldhuisen DJ, Dickstein K, Cohen-Solal A, et al. Randomized, double-blind, placebo-controlled study to evaluate the effect of two dosing regimens of darbepoetin alfa in patients with heart failure and anaemia. *Eur Heart J*. 2007;28:2208-16.
183. Ghali JK, Anand IS, Abraham WT, et al. Randomized double-blind trial of darbepoetin alfa in patients with symptomatic heart failure and anemia. *Circulation*. 2008;117:526-35.
184. Kotecha D, Ngo K, Walters JA, et al. Erythropoietin as a treatment of anemia in heart failure: systematic review of randomized trials. *Am Heart J*. 2011;161:822-31.
185. Bennett CL, Silver SM, Djulbegovic B, et al. Venous thromboembolism and mortality associated with recombinant erythropoietin and darbepoetin administration for the treatment of cancer-associated anemia. *JAMA*. 2008;299:914-24.
186. Bohlius J, Wilson J, Seidenfeld J, et al. Recombinant human erythropoietins and cancer patients: updated meta-analysis of 57 studies including 9353 patients. *J Natl Cancer Inst*. 2006;98:708-14.
187. Pfeffer MA, Burdman EA, Chen CY, et al. A trial of darbepoetin alfa in type 2 diabetes and chronic kidney disease. *N Engl J Med*. 2009;361:2019-32.
188. Szczech LA, Barnhart HX, Inrig JK, et al. Secondary analysis of the CHOIR trial epoetin-alpha dose and achieved hemoglobin outcomes. *Kidney Int*. 2008;74:791-8.
189. Xie X, Atkins E, Lv J, et al. Effects of intensive blood pressure lowering on cardiovascular and renal outcomes: updated systematic review and meta-analysis. *Lancet*. 2016;387:435-43.
190. Thomopoulos C, Parati G, Zanchetti A. Effects of blood pressure lowering on outcome incidence in hypertension: 7. Effects of more vs. less intensive blood pressure lowering and different achieved blood pressure levels - updated overview and meta-analyses of randomized trials. *J Hypertens*. 2016;34:613-22.
191. Wright JT Jr, Williamson JD, Whelton PK, et al. A Randomized Trial of Intensive versus Standard Blood-Pressure Control. *N Engl J Med*. 2015;373:2103-16.
192. Williamson JD, Supiano MA, Applegate WB, et al. Intensive vs standard blood pressure control and cardiovascular disease outcomes in adults aged ≥ 75 years: A randomized clinical trial. *JAMA*. 2016;315:2673-82.
193. Lv J, Ehteshami P, Sarnak MJ, et al. Effects of intensive blood pressure lowering on the progression of chronic kidney disease: a systematic review and meta-analysis. *CMAJ*. 2013;185:949-57.
194. Deleted in press.
195. Aronow WS, Fleg JL, Pepine CJ, et al. ACCF/AHA 2011 expert consensus document on hypertension in the elderly: a report of the American College of Cardiology Foundation Task Force on Clinical Expert Consensus Documents. Developed in collaboration with the American Academy of Neurology, American Geriatrics Society, American Society for Preventive Cardiology, American Society of Hypertension, American Society of Nephrology, Association of Black Cardiologists, and European Society of Hypertension. *J Am Coll Cardiol*. 2011;57:2037-114.
196. Law MR, Morris JK, Wald NJ. Use of blood pressure lowering drugs in the prevention of cardiovascular disease: meta-analysis of 147 randomised trials in the context of expectations from prospective epidemiological studies. *BMJ*. 2009;338:b1665.
197. Aronow WS, Ahn C, Kronzon I. Effect of propranolol versus no propranolol on total mortality plus nonfatal myocardial infarction in older patients with prior myocardial infarction, congestive heart failure, and left ventricular ejection fraction $\geq 40\%$ treated with diuretics plus angiotensin-converting enzyme inhibitors. *Am J Cardiol*. 1997;80:207-9.
198. van Veldhuisen DJ, Cohen-Solal A, Bohm M, et al. Beta-blockade with nebivolol in elderly heart failure patients with impaired and preserved left ventricular ejection fraction: Data From SENIORS (Study of Effects of Nebivolol Intervention on Outcomes and Rehospitalization in Seniors With Heart Failure). *J Am Coll Cardiol*. 2009;53:2150-8.
199. Piller LB, Baraniuk S, Simpson LM, et al. Long-term follow-up of participants with heart failure in the antihypertensive and lipid-lowering treatment to prevent heart attack trial (ALLHAT). *Circulation*. 2011;124:1811-8.
200. Arzt M, Floras JS, Logan AG, et al. Suppression of central sleep apnea by continuous positive airway pressure and transplant-free survival in heart failure: a post hoc analysis of the Canadian Continuous Positive Airway Pressure for Patients with Central Sleep Apnea and Heart Failure Trial (CANPAP). *Circulation*. 2007;115:3173-80.
201. Bradley TD, Logan AG, Kimoff RJ, et al. Continuous positive airway pressure for central sleep apnea and heart failure. *N Engl J Med*. 2005;353:2025-33.
202. MacDonald M, Fang J, Pittman SD, et al. The current prevalence of sleep disordered breathing in congestive heart failure patients treated with beta-blockers. *J Clin Sleep Med*. 2008;4:38-42.
203. Cowie MR, Woehrle H, Wegscheider K, et al. Adaptive Servo-Ventilation for Central Sleep Apnea in Systolic Heart Failure. *N Engl J Med*. 2015;373:1095-105.
204. McEvoy RD, Antic NA, Heeley E, et al. CPAP for prevention of cardiovascular events in obstructive sleep apnea. *N Engl J Med*. 2016;375:919-31.
205. Holmqvist F, Guan N, Zhu Z, et al. Impact of obstructive sleep apnea and continuous positive airway pressure therapy on outcomes in patients with atrial fibrillation-Results from the Outcomes Registry for Better Informed Treatment of Atrial Fibrillation (ORBIT-AF). *Am Heart J*. 2015;169:647-54.

KEY WORDS ACC/AHA Clinical Practice Guidelines, angioedema, angiotensin-converting enzyme inhibitors, angiotensin receptor blockers, angiotensin receptor-neprilysin inhibitor, beta blockers, ferric carboxymaltose, focused update, heart failure, hypertension, iron deficiency, ivabradine, natriuretic peptides, natriuretic peptide biomarker, sleep apnea

APPENDIX 1. AUTHOR RELATIONSHIPS WITH INDUSTRY AND OTHER ENTITIES (RELEVANT)—2017 ACC/AHA/HFSA FOCUSED UPDATE OF THE 2013 ACCF/AHA GUIDELINE FOR THE MANAGEMENT OF HEART FAILURE (DECEMBER 2015)

Committee Member	Employment	Consultant	Speakers Bureau	Ownership/ Partnership/ Principal	Personal Research	Institutional, Organizational, or Other Financial Benefit	Expert Witness	Voting Recusals By Section*
Clyde W. Yancy (Chair)	Northwestern University Feinberg School of Medicine, Division of Cardiology—Professor of Medicine and Chief; Diversity and Inclusion—Vice Dean	None	None	None	None	None	None	None
Mariell Jessup (Vice Chair)	Fondation Leducq—Chief Scientific Officer	None	None	None	None	None	None	None
Biykem Bozkurt	Baylor College of Medicine, Department of Medicine—Professor of Medicine; Cardiology Section, DeBakey VA Medical Center—Chief; The Mary and Gordon Cain Chair & W.A. "Tex" and Deborah Moncrief, Jr.—Chair; Winters Center for Heart Failure Research—Director; Cardiovascular Research Institute—Associate Director	None	None	None	■ Novartis	None	None	7.3.2.10, 7.3.2.11, 7.3.3, and 9.5.
Javed Butler	Stony Brook University—Division Chief of Cardiology	■ Bayer† ■ Boehringer Ingelheim ■ CardioCell† ■ Luitpold ■ Medtronic ■ Merck† ■ Novartis† ■ Relypsa† ■ Takeda ■ Trevena† ■ Z Pharma ■ Zensun	■ Novartis†	None	■ Amgen (DSMB)†	None	None	7.3.2.10, 7.3.2.11, 7.3.3, and 9.5.
Donald E. Casey, Jr	Thomas Jefferson College of Population Health— Faculty; Alvarez & Marsal IPO4Health—Principal and Founder	None	None	None	None	None	None	None
Monica M. Colvin	University of Michigan—Associate Professor of Medicine, Cardiology	None	None	None	None	None	None	None
Mark H. Drazner	University of Texas Southwestern Medical Center—Professor, Internal Medicine	None	None	None	None	None	None	None
Gerasimos S. Filippatos	National and Kapodistrian University of Athens; Attikon University Hospital, Department of Cardiology, Heart Failure Unit—Professor of Cardiology	None	None	None	■ Bayer† ■ Bayer (DSMB) ■ Novartis† ■ Servier Pharmaceuticals† ■ Vifor	None	None	7.3.2.10, 7.3.2.11, 7.3.3, 9.2, and 9.5.

Continued on the next page

APPENDIX 1. CONTINUED

Committee Member	Employment	Consultant	Speakers Bureau	Ownership/ Partnership/ Principal	Personal Research	Institutional, Organizational, or Other Financial Benefit	Expert Witness	Voting Recusals By Section*
Gregg C. Fonarow	Ahmanson-UCLA Cardiomyopathy Center—Director; UCLA Division of Cardiology—Co-Chief	■ Amgen ■ Janssen Pharmaceuticals ■ Novartis†	None	None	■ Novartis†	None	None	7.3.2.10, 7.3.2.11, 7.3.3, and 9.5.
Michael M. Givertz	Brigham and Women's Hospital—Professor of Medicine	■ Merck ■ Novartis	None	None	None	None	None	7.3.2.10, 7.3.2.11, 7.3.3, and 9.5.
Steven M. Hollenberg	Cooper University Hospital—Director, Coronary Care Unit, Professor of Medicine	None	None	None	None	None	None	None
JoAnn Lindenfeld	Vanderbilt Heart and Vascular Institute—Director, Advanced Heart Failure and Transplant Section—Professor of Medicine	■ Abbott ■ Janssen Pharmaceuticals ■ Novartis ■ Relypsa† ■ ResMed†	None	None	■ AstraZeneca ■ Novartis†	None	None	6.3, 7.3.2.10, 7.3.2.11, 7.3.3, 9.5, and 9.6.
Frederick A. Masoudi	University of Colorado, Anschutz Medical Campus—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 Director, Preventive Cardiology	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
Lynne Warner Stevenson	Brigham and Women's Hospital Cardiovascular Division—Director, Cardiomyopathy and Heart Failure Program	None	None	None	■ Novartis—PARENT trial (PI) ■ NHLBI—INTERMACS (Co-PI)	None	None	7.3.2.10, 7.3.2.11, 7.3.3, and 9.5.
Cheryl Westlake	Azusa Pacific University, School of Nursing, Doctoral Programs—Professor	None	None	None	None	None	None	None

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 ≥\$5,000 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 ACC/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.

†Significant relationship.

ACC indicates American College of Cardiology; ACCF, American College of Cardiology Foundation; AHA, American Heart Association; DCRI, Duke Clinical Research Institute; DSMB, data safety monitoring board; HFSA, Heart Failure Society of America; NHLBI, National Heart, Lung, and Blood Institute; INTERMACS, Interagency Registry for Mechanically Assisted Circulatory Support; PARENT, Pulmonary artery pressure reduction with entresto; UCLA, University of California, Los Angeles; and VA, Veterans Affairs.

APPENDIX 2. REVIEWER RELATIONSHIPS WITH INDUSTRY AND OTHER ENTITIES (COMPREHENSIVE)—2017 ACC/AHA/HFSA FOCUSED UPDATE OF THE 2013 ACCF/AHA GUIDELINE FOR THE MANAGEMENT OF HEART FAILURE (OCTOBER 2016)

Reviewer	Representation	Employment	Consultant	Speakers Bureau	Ownership/ Partnership/ Principal	Personal Research	Institutional, Organizational, or Other Financial Benefit	Expert Witness
Kim K. Birtcher	Official Reviewer—ACC/AHA Task Force on Clinical Practice Guidelines	University of Houston College of Pharmacy—Clinical Professor	■ Jones & Bartlett Learning	None	None	None	None	None
Akshay S. Desai	Official Reviewer—HFSA	Brigham and Women's Hospital—Director, Heart Failure Disease Management, Advanced Heart Disease Section, Cardiovascular Division; Associate Professor of Medicine, Harvard Medical School	■ Medscape Cardiology* ■ Merck ■ Novartis* ■ Relypsa* ■ St. Jude Medical*	None	None	None	■ Novartis* ■ Thoratec	None
Anita Deswal	Official Reviewer—AHA	Michael E. DeBakey VA Medical Center—Chief of Cardiology; Director, Heart Failure Program; Baylor College of Medicine—Professor of Medicine	None	None	None	■ NIH*	■ AHA ■ AHA (GWTG Steering Committee)† ■ HFSA†	None
Dipti Itchhaporia	Official Reviewer—ACC Board of Trustees	Newport Coast Cardiology—Robert and Georgia Roth Endowed Chair for Excellence in Cardiac Care; Director of Disease Management	None	None	None	None	■ St. Jude Medical	None
Ileana L. Piña	Official Reviewer—AHA	Montefiore Medical Center—Associate Chief for Academic Affairs, Cardiology; Professor of Medicine & Epidemiology and Population Health—Albert Einstein College of Medicine	■ Relypsa	None	None	None	None	None
Geetha Raghuvver	Official Reviewer—ACC Board of Governors	University of Missouri-Kansas City School of Medicine—Professor of Pediatrics; Children's Mercy Hospital—Pediatric Cardiology	None	None	None	None	None	None
James E. Udelson	Official Reviewer—HFSA	Tufts Medical Center—Chief, Division of Cardiology	■ Lantheus Medical Imaging	None	None	■ Gilead (DSMB) ■ GlaxoSmithKline (DSMB) ■ NHLBI ■ Otsuka	■ Abbott Laboratories ■ AHA* ■ Circulation/Circulation: Heart Failure† ■ HFSA (Executive Council)† ■ Pfizer/GlaxoSmithKline ■ Sunshine Heart	None
Mary Norine Walsh	Official Reviewer—ACC Board of Trustees	St Vincent Heart Center of Indiana—Medical Director, Heart Failure and Cardiac Transplantation	None	None	None	None	■ Corvia Medical ■ Otsuka ■ PCORI ■ Thoratec	None
David A. Baran	Organizational Reviewer—ISHLT	Newark Beth Israel Medical Center—Director of Heart Failure and Transplant Research	■ Maquet ■ Otsuka*	■ Novartis	None	■ XDx* ■ NIH*	None	None

Continued on the next page

APPENDIX 2. CONTINUED

Reviewer	Representation	Employment	Consultant	Speakers Bureau	Ownership/ Partnership/ Principal	Personal Research	Institutional, Organizational, or Other Financial Benefit	Expert Witness
Kenneth Casey	Organizational Reviewer—CHEST	Wm. S. Middleton Memorial Veterans Hospital—Director, Sleep Medicine	None	None	None	None	■ CHEST	None
M. Fuad Jan	Organizational Reviewer—CHEST	Aurora Advanced Healthcare—Cardiologist	None	None	None	None	None	None
Kenneth W. Lin	Organizational Reviewer—AAFP	Georgetown University School of Medicine—Clinician Educator Track, Associate Professor	None	None	None	None	None	None
Joaquin E. Cigarroa	Content Reviewer—ACC/AHA Task Force on Clinical Practice Guidelines	Oregon Health & Science University—Clinical Professor of Medicine	None	None	None	None	■ ACC/AHA† ■ AHA† ■ ASA† ■ Catheterization and Cardiovascular Intervention† ■ NIH ■ Portland Metro Area AHA (President)† ■ SCAI Quality Interventional Council†	None
Lee A. Fleisher	Content Reviewer—ACC/AHA Task Force on Clinical Practice Guidelines	University of Pennsylvania Health System—Robert Dunning Dripps Professor of Anesthesiology and Critical Care; Chair, Department of Anesthesiology & Critical Care	■ Blue Cross/Blue Shield* ■ NQF† ■ Yale University	None	None	■ Johns Hopkins (DSMB)	■ Association of University Anesthesiologists† ■ NIH	None
Samuel S. Gidding	Content Reviewer—ACC/AHA Task Force on Clinical Practice Guidelines	Nemours/Alfred I. duPont Hospital for Children—Chief, Division of Pediatric Cardiology	■ FH Foundation† ■ International FH Foundation†	None	None	■ FH Foundation† ■ NIH*	None	None
James L. Januzzi	Content Reviewer	Massachusetts General Hospital—Hutter Family Professor of Medicine in the Field of Cardiology	■ Critical Diagnostics* ■ Novartis* ■ Phillips ■ Roche Diagnostics* ■ Sphingotec*	None	None	■ Amgen (DSMB) ■ Boeringer ■ Ingelheim (DSMB)* ■ Janssen Pharmaceuticals (DSMB) ■ Prevencio*	None	None
José A. Joglar	Content Reviewer—ACC/AHA Task Force on Clinical Practice Guidelines	UT Southwestern Medical Center—Professor of Internal Medicine; Clinical Cardiac Electrophysiology—Program Director	None	None	None	None	None	None
Edward K. Kasper	Content Reviewer	Johns Hopkins Cardiology—E. Cowles Andrus Professor in Cardiology	None	None	None	None	None	None
Wayne C. Levy	Content Reviewer	University of Washington—Professor of Medicine	■ Abbott Laboratories ■ Biotronik ■ GE Healthcare ■ HeartWare ■ PharminIN	None	None	■ NIH ■ Novartis* ■ St. Jude Medical*	■ Amgen* ■ AHA ■ HeartWare* ■ Novartis* ■ Resmed* ■ Thoratec	None

Continued on the next page

APPENDIX 2. CONTINUED

Reviewer	Representation	Employment	Consultant	Speakers Bureau	Ownership/ Partnership/ Principal	Personal Research	Institutional, Organizational, or Other Financial Benefit	Expert Witness
Judith E. Mitchell	Content Reviewer	SUNY Downstate Medical Center—Director/Heart Failure Center; SUNY Downstate College of Medicine—Associate Professor of Medicine	None	None	None	None	■ Association of Black Cardiologists†	None
Sean P. Pinney	Content Reviewer—ACC Heart Failure and Transplant Council	Mount Sinai School of Medicine—Associate Professor of Medicine, Cardiology	■ Acorda Therapeutics ■ Thoratec ■ XDx	None	None	■ Thoratec† ■ NIH†	None	None
Randall C. Starling	Content Reviewer—ACC Heart Failure and Transplant Council	Cleveland Clinic Department of Cardiovascular Medicine—Vice Chairman, Department of Cardiovascular Medicine; Section Head, Heart Failure & Cardiac Transplant	■ BioControl ■ Medtronic ■ Novartis	None	None	■ Medtronic ■ NIH* ■ Novartis† ■ St. Jude Medical†	■ St. Jude Medical	None
W.H. Wilson Tang	Content Reviewer	Cleveland Clinic Foundation—Assistant Professor of Medicine	None	None	None	■ NIH*	■ Alnylam Pharmaceuticals ■ NIH ■ NHLBI ■ Roche ■ Novartis ■ Thoratec	None
Emily J. Tsai	Content Reviewer	Columbia University College of Physicians & Surgeons—Assistant Professor of Medicine, Division of Cardiology	None	None	None	■ Bayer† ■ Bristol-Myers Squibb† ■ NHLBI*	None	None
Duminda N. Wijeyesundera	Content Reviewer—ACC/AHA Task Force on Clinical Practice Guidelines	Li Ka Shing Knowledge Institute of St. Michael's Hospital—Scientist; University of Toronto—Assistant Professor, Department of Anesthesia and Institute of Health Policy Management and Evaluation	None	None	None	■ CIHR (DSMB)† ■ CIHR* ■ Heart and Stroke Foundation of Canada* ■ Ministry of Health & Long-term Care of Ontario* ■ PCORI DSMB)†	None	None

This table represents the relationships of reviewers with industry and other entities that were disclosed at the time of peer review, including those not deemed to be relevant to this document. 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 ≥\$5,000 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.

American College of Physicians did not provide a peer reviewer for this document.

*Significant relationship.

†No financial benefit.

AAFP indicates American Academy of Family Physicians; ACC, American College of Cardiology; ACCF, American College of Cardiology Foundation; AHA, American Heart Association; ASA, American Stroke Association; CHEST, American College of Chest Physicians; CIHR, Canadian Institutes of Health Research; DSMB, data safety monitoring board; FH, familial hypercholesterolemia; GWTG, Get With The Guidelines; HFSA, Heart Failure Society of America; ISHLT, International Society for Heart and Lung Transplantation; NIH, National Institutes of Health; NHLBI, National Heart, Lung, and Blood Institute; NQF, National Quality Forum; PCORI, Patient-Centered Outcomes Research Institute; SCAI, Society for Cardiac Angiography and Interventions; SUNY, State University of New York; UT, University of Texas; and VA, Veterans Affairs.

APPENDIX 3. ABBREVIATIONS

ACE = angiotensin-converting enzyme

ARB = angiotensin-receptor blocker

ARNI = angiotensin receptor-neprilysin inhibitor

BNP = B-type natriuretic peptide

BP = blood pressure

COR = Class of Recommendation

CPAP = continuous positive airway pressure

EF = ejection fraction

GDMT = guideline-directed management and therapy

HFpEF = heart failure with preserved ejection fraction

HFrfEF = heart failure with reduced ejection fraction

LOE = Level of Evidence

LVEF = left ventricular ejection fraction

NT-proBNP = N-terminal pro-B-type natriuretic peptide

QoL = quality of life

RCT = randomized controlled trial
