

# 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

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## Key Words:

AHA Scientific Statements ■ 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

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## 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<sup>1,2</sup> 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.<sup>3</sup>

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<sup>4</sup> and other methodology articles.<sup>5–8</sup>

## 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.<sup>4–7</sup> 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).<sup>4–6</sup>

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Chair, ACC/AHA Task Force on Clinical  
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## 1. INTRODUCTION

The purpose of this focused update is to update the "2013 ACCF/AHA Guideline for the Management of Heart Failure"<sup>9</sup> (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,"<sup>10</sup> 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

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

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.

for the Diagnosis and Treatment of Acute and Chronic Heart Failure.”<sup>11</sup>

### 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<sup>9</sup> 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.<sup>4–6</sup> 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.

## 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<sup>12</sup> but not NT-proBNP levels.<sup>13</sup> 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,<sup>12,14</sup> with the reduction in 1 study being associated with improved clinical outcomes.<sup>12</sup>

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 (eg, dyspnea, weight gain) in the setting of chronic ambulatory HF<sup>15–21</sup> or in the setting of acute care with decompensated HF<sup>22–30</sup> especially when the cause of dyspnea is unclear. The role of natriuretic peptide biomarkers in population screening to detect incident HF is emerging.<sup>31–37</sup> Elevated plasma levels of natriuretic peptide biomarkers are associated with a wide variety of cardiac and noncardiac causes (Table 2).<sup>38–42</sup> Obesity may be associated with lower natriuretic peptide concentrations, and this may modestly reduce diagnostic sensitivity in morbidly obese patients.<sup>42</sup>

**Table 2. Selected Potential Causes of Elevated Natriuretic Peptide Levels<sup>38–41</sup>**

| 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.<sup>9</sup>

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

Because of the absence of clear and consistent evidence for improvement in mortality and cardiovascular outcomes,<sup>43–62</sup> 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.<sup>63</sup> 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.<sup>64</sup>

In addition to natriuretic peptides and troponins,<sup>65–67</sup> multiple other biomarkers, including those of inflam-

mation, oxidative stress, vascular dysfunction, and myocardial and matrix remodeling, have been implicated in HF.<sup>68–71</sup> 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.<sup>72–74</sup> 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.<sup>75,76</sup> Several emerging biomarkers await validation with well-defined outcome measures and prognostic accuracy before they can reach the clinical arena.<sup>77–84</sup>

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.

### 6.3.1 Biomarkers for Prevention: Recommendation

| Biomarkers: Recommendation for Prevention of HF |            |  |  |
|---|------------|--|--|
| COR   | LOE        | Recommendation   | Comment/Rationale  |
| <b>Ia</b>                                       | <b>B-R</b> | <b>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.</b> <sup>85,86</sup>   | <b>NEW:</b> 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]), <sup>85</sup> patients at risk of HF (identified by the presence of hypertension, diabetes mellitus, or known vascular disease [eg, 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 $\geq 50$ 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. <sup>85</sup> 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. <sup>86</sup> 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. |  |

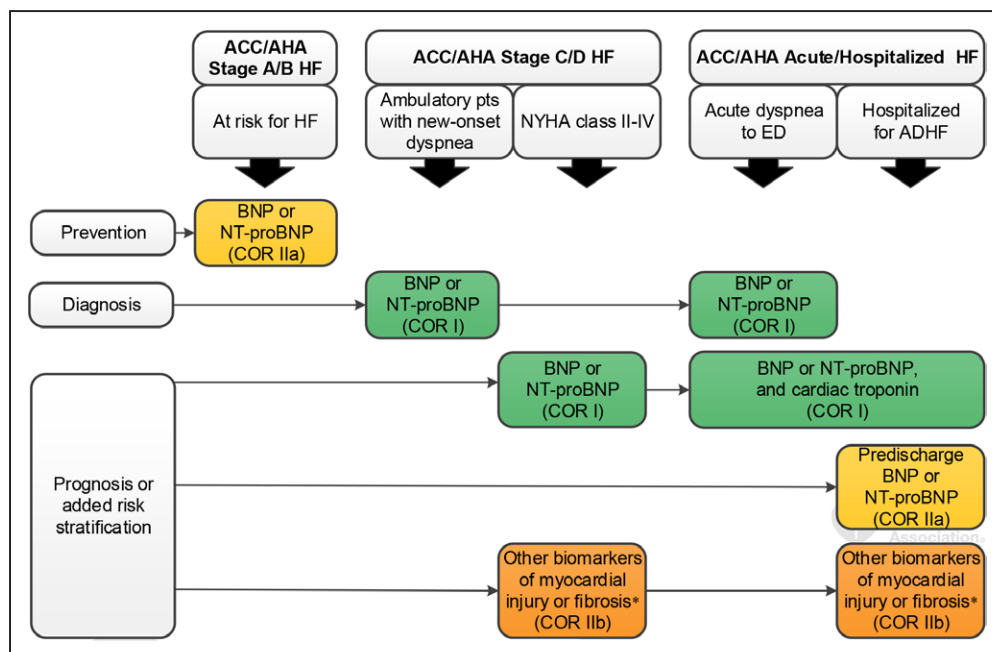
### 6.3.2 Biomarkers for Diagnosis: Recommendation

| Biomarkers: Recommendation for Diagnosis |          |  |  |
|--|----------|--|--|
| COR                                      | LOE      | Recommendation   | Comment/Rationale  |
| <b>I</b>                                 | <b>A</b> | <b>In patients presenting with dyspnea, measurement of natriuretic peptide biomarkers is useful to support a diagnosis or exclusion of HF.</b> <sup>15–24,28–30</sup>  | <b>MODIFIED:</b> 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. <sup>15–21</sup> 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. <sup>20</sup> 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). <sup>38–41</sup> |  |

### 6.3.3 Biomarkers for Prognosis or Added Risk Stratification: Recommendations

| Biomarkers: Recommendations for Prognosis |          |  |                                      |
|---|----------|--|--------------------------------------|
| COR                                       | LOE      | Recommendations  | Comment/Rationale                    |
| <b>I</b>                                  | <b>A</b> | <b>Measurement of BNP or NT-proBNP is useful for establishing prognosis or disease severity in chronic HF.</b> <sup>16,87–92</sup> | 2013 recommendation remains current. |

| Biomarkers: Recommendations for Prognosis (Continued) |             |   |   |
|---|-------------|---|---|
| COR   | LOE         | Recommendations   | Comment/Rationale   |
| <b>I</b>  | <b>A</b>    | <b>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.</b> <sup>27,93–100</sup>   | <b>MODIFIED:</b> Current recommendation emphasizes that it is admission levels of natriuretic peptide biomarkers that are useful. |
| See Online Data Supplements A and B.                  |             | <p>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.<sup>20,27,29,93–101</sup> 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.<sup>95,99,102,103</sup></p> <p>Studies have demonstrated incremental prognostic value of these biomarkers to standard approaches of cardiovascular disease risk assessment.<sup>29,95</sup> However, there were differences in the risk prediction models, assay cutpoints, and lengths of follow-up.<sup>29</sup> 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.</p> |   |
| <b>IIa</b>  | <b>B-NR</b> | <b>During a HF hospitalization, a predischARGE natriuretic peptide level can be useful to establish a postdischarge prognosis.</b> <sup>93,96,104–113</sup>   | <b>NEW:</b> Current recommendation reflects new observational studies.  |
| See Online Data Supplements A and B.                  |             | <p>PredischARGE 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.<sup>93,96,104–113</sup> Several studies have suggested that predischARGE natriuretic peptide biomarker levels had higher reclassification and discrimination value than clinical variables in predicting outcomes.<sup>96,106,108–111</sup> Patients with higher predischARGE levels and patients who do not have a decrease in natriuretic peptide biomarker levels during hospitalization have worse outcomes.<sup>96,106,108–111</sup> 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,<sup>93,107,112,113</sup> 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 predischARGE value or relative changes does not imply the necessity for serial and repeated biomarker measurements during hospitalization.</p>                     |   |
| <b>IIb</b>  | <b>B-NR</b> | <b>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.</b> <sup>27,95,98,99,103,114–119</sup>  | <b>MODIFIED:</b> 2013 recommendations have been combined into prognosis section, resulting in LOE change from A to B-NR.          |
| See Online Data Supplements A and B.                  |             | <p>Biomarkers of myocardial fibrosis (eg, 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.<sup>117,119–126</sup> A combination of biomarkers may ultimately prove to be more informative than single biomarkers.<sup>127</sup></p>   |   |



**Figure 1. Biomarkers Indications for Use.**

Colors correspond to COR in Table 1. \*Other biomarkers of injury or fibrosis include soluble ST2 receptor, galectin-3, and high-sensitivity troponin. ACC indicates American College of Cardiology; AHA, American Heart Association; ADHF, acute decompensated heart failure; BNP, B-type natriuretic peptide; COR, Class of Recommendation; ED, emergency department; HF, heart failure; NT-proBNP, N-terminal pro-B-type natriuretic peptide; NYHA, New York Heart Association; and pts, patients.

## 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  | <b>The clinical strategy of inhibition of the renin-angiotensin system with ACE inhibitors (Level of Evidence: A),<sup>128–133</sup> OR ARBs (Level of Evidence: A),<sup>134–137</sup> OR ARNI (Level of Evidence: B-R)<sup>138</sup> in conjunction with evidence-based beta blockers,<sup>9,139,140</sup> and aldosterone antagonists in selected patients,<sup>141,142</sup> is recommended for patients with chronic HFrEF to reduce morbidity and mortality.</b>  | <b>NEW:</b> New clinical trial data prompted clarification and important updates. |
|   | ARB: A    |  |   |
|   | ARNI: B-R |  |   |
| See Online Data Supplements 1, 2, 18-20.  |           | <p>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.<sup>128–133</sup> 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.</p> <p>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<sup>134–137</sup> to reduce morbidity and mortality, especially in ACE inhibitor–intolerant patients.</p> <p>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%.<sup>138</sup> 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.</p> |   |
| I   | ACE-I: A  | <b>The use of ACE inhibitors is beneficial for patients with prior or current symptoms of chronic HFrEF to reduce morbidity and mortality.<sup>128–133,143</sup></b>   | 2013 recommendation repeated for clarity in this section.                         |
| See Online Data Supplement 18.  |           | <p>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.<sup>128–133</sup> Data suggest that there are no differences among available ACE inhibitors in their effects on symptoms or survival.<sup>143</sup> 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 (&gt;5.0 mEq/L). Angioedema occurs in &lt;1% of patients who take an ACE inhibitor, but it occurs more frequently in blacks and women.<sup>144</sup> 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.</p> <p>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></p>  |   |
| I   | ARB: A    | <b>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.<sup>134–137,145,146</sup></b>   | 2013 recommendation repeated for clarity in this section.                         |
| See Online Data Supplements 2 and 19.   |           | <p>ARBs have been shown to reduce mortality and HF hospitalizations in patients with HFrEF in large RCTs.<sup>134–137</sup> 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.<sup>145,146</sup> 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.</p> <p>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 (&gt;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.</p> <p>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></p>  |   |

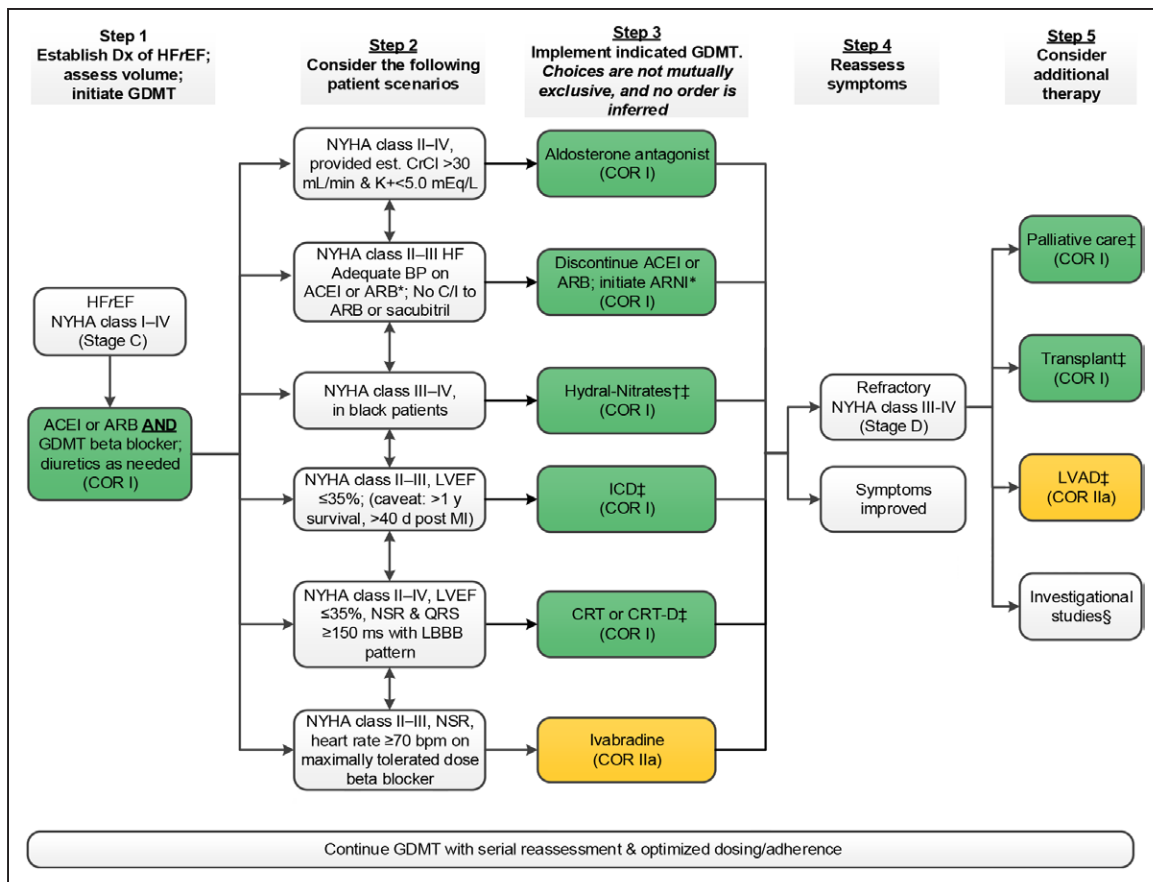


| Recommendations for Renin-Angiotensin System Inhibition With ACE Inhibitor or ARB or ARNI (Continued) |           |  |  |
|---|-----------|--|--|
| COR   | LOE       | Recommendations  | Comment/Rationale  |
| I   | ARNI: B-R | <b>In patients with chronic symptomatic HFrEF NYHA class II or III who tolerate an ACE inhibitor or ARB, replacement by an ARNI is recommended to further reduce morbidity and mortality.<sup>138</sup></b>  | <b>NEW:</b> 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. <sup>129</sup> 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. <sup>147</sup> 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. <sup>14</sup> |  |
| III: Harm   | B-R       | <b>ARNI should not be administered concomitantly with ACE inhibitors or within 36 hours of the last dose of an ACE inhibitor.<sup>148,149</sup></b>  | <b>NEW:</b> 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 <sup>148,149</sup> 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. <sup>149,150</sup> An ARNI should not be administered within 36 hours of switching from or to an ACE inhibitor.   |  |
| III: Harm   | C-EO      | <b>ARNI should not be administered to patients with a history of angioedema.</b>   | <b>NEW:</b> 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. <sup>148</sup> In a very large RCT of hypertensive patients, omapatrilat was associated with a 3-fold increased risk of angioedema as compared with enalapril. <sup>149</sup> Blacks and smokers were particularly at risk. The high incidence of angioedema ultimately led to cessation of the clinical development of omapatrilat. <sup>151,152</sup> In light of these observations, angioedema was an exclusion criterion in the first large trial assessing ARNI therapy in patients with hypertension <sup>153</sup> and then in the large trial that demonstrated clinical benefit of ARNI therapy in HFrEF. <sup>138</sup> 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 | <b>Ivabradine can be beneficial to reduce HF hospitalization for patients with symptomatic (NYHA class II-III) stable chronic HFrEF (LVEF ≤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.<sup>154-157</sup></b>  | <b>NEW:</b> 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. <sup>155</sup> 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) ≤35%, in sinus rhythm with a resting heart rate of ≥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. <sup>9,139,140,155</sup> 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. <sup>155</sup> |                                      |

\*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."<sup>10</sup>



**Figure 2. Treatment of HF/EF 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.<sup>9</sup> §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; HF/EF, 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.

### 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. <sup>164,165</sup>                    | 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.  |
| IIa                               | 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.  |
| IIa                               | 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). |
| IIa                               | 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.  |

| Recommendations for Stage C HFpEF (Continued)  |            |   |   |
|--|------------|---|---|
| COR  | LOE        | Recommendations   | Comment/Rationale   |
| <b>IIb</b>   | <b>B-R</b> | <b>In appropriately selected patients with HFpEF (with EF <math>\geq</math>45%, elevated BNP levels or HF admission within 1 year, estimated glomerular filtration rate <math>&gt;</math>30 mL/min, creatinine <math>&lt;</math>2.5 mg/dL, potassium <math>&lt;</math>5.0 mEq/L), aldosterone receptor antagonists might be considered to decrease hospitalizations.<sup>83,166,167</sup></b> | <b>NEW:</b> Current recommendation reflects new RCT data.       |
| See Online Data Supplement C.  |            |   |   |
| <p>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.<sup>83,168</sup></p> <p>The TOPCAT (Treatment of Preserved Cardiac Function Heart Failure With an Aldosterone Antagonist) trial<sup>166</sup> 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.<sup>166</sup> An unusual amount of regional variation was seen in this trial, prompting a post-hoc analysis<sup>167</sup> 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.<sup>169,170</sup> 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] <math>\geq</math>45%, elevated BNP level or HF admission within 1 year, estimated glomerular filtration rate <math>&gt;</math>30 mL/min creatinine <math>&lt;</math>2.5 mg/dL, and potassium <math>&lt;</math>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.</p> <p>With regard to the use of mineralocorticoid receptor antagonists, creatinine should be <math>&lt;</math>2.5 mg/dL in men or <math>&lt;</math>2.0 mg/dL in women (or estimated glomerular filtration rate <math>&gt;</math>30 mL/min) and potassium should be <math>&lt;</math>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.</p> |            |   |   |
| <b>IIb</b>   | <b>B</b>   | <b>The use of ARBs might be considered to decrease hospitalizations for patients with HFpEF.<sup>169</sup></b>  | 2013 recommendation remains current.                            |
| <b>III: No Benefit</b>   | <b>B-R</b> | <b>Routine use of nitrates or phosphodiesterase-5 inhibitors to increase activity or QoL in patients with HFpEF is ineffective.<sup>171,172</sup></b>   | <b>NEW:</b> Current recommendation reflects new data from RCTs. |
| See Online Data Supplement C.  |            |   |   |
| <p>Nitrate therapy can reduce pulmonary congestion and improve exercise tolerance in patients with HFpEF. However, the NEAT-HFpEF (Nitrate's Effect on Activity Tolerance in Heart Failure With Preserved Ejection Fraction) trial<sup>171</sup> randomized 110 patients with EF <math>\geq</math>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<sup>172</sup> randomized 216 patients with EF <math>\geq</math>50% on stable HF therapy and with reduced exercise tolerance (peak observed <math>\dot{V}_{O_2}</math> <math>&lt;</math>60% of predicted) to phosphodiesterase-5 inhibition with sildenafil or placebo. This study did not show improvement in oxygen consumption or exercise tolerance.</p>  |            |   |   |
| <b>III: No Benefit</b>   | <b>C</b>   | <b>Routine use of nutritional supplements is not recommended for patients with HFpEF.</b>   | 2013 recommendation remains current.                            |

## 9. IMPORTANT COMORBIDITIES IN HF

### 9.2. Anemia: Recommendations

| Recommendations for Anemia   |            |  |   |
|--|------------|--|---|
| COR  | LOE        | Recommendations  | Comment/Rationale   |
| <b>IIb</b>   | <b>B-R</b> | <b>In patients with NYHA class II and III HF and iron deficiency (ferritin <math>&lt;</math>100 ng/mL or 100 to 300 ng/mL if transferrin saturation is <math>&lt;</math>20%), intravenous iron replacement might be reasonable to improve functional status and QoL.<sup>173,174</sup></b> | <b>NEW:</b> New evidence consistent with therapeutic benefit. |
| See Online Data Supplement D.  |            |  |   |
| <p>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<sup>173</sup> 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<sup>174</sup> 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.<sup>175</sup> 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.</p> |            |  |   |

| Recommendations for Anemia (Continued)   |     |   |  |
|--|-----|---|--|
| COR  | LOE | Recommendations   | Comment/Rationale  |
| III: No Benefit  | B-R | In patients with HF and anemia, erythropoietin-stimulating agents should not be used to improve morbidity and mortality. <sup>176</sup> | <b>NEW:</b> Current recommendation reflects new evidence demonstrating absence of therapeutic benefit. |
| See Online Data Supplement D.  |     |   |  |
| 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, <sup>177–182</sup> but results have varied <sup>183</sup> 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 <sub>2</sub> , NYHA functional status, EF, BNP, HF-related hospitalizations, and QoL, <sup>184</sup> in the STAMINA-HeFT (Study of Anemia in Heart Failure) trial, <sup>183</sup> darbepoetin alfa was not associated with significant clinical benefits. In the largest RCT to date (n=2278), 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. <sup>176,185–188</sup> 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. |     |   |  |

**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 |
|--|--|--|---|------------|
| <i>ACE inhibitors</i>                                    |  |  |   |            |
| 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   | —          |
| <i>ARBs</i>  |  |  |   |            |
| 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        |
| <i>ARNI</i>  |  |  |   |            |
| 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>I<sub>1</sub> channel inhibitor</i>                   |  |  |   |            |
| Ivabradine   | 5 mg BID   | 7.5 mg BID   | 6.4 mg BID (at 28 d) 6.5 mg BID (at 1 y)                    | 155–157    |
| <i>Aldosterone antagonists</i>                           |  |  |   |            |
| 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        |
| <i>Beta blockers</i>                                     |  |  |   |            |
| 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        |
| <i>Isosorbide dinitrate and hydralazine</i>              |  |  |   |            |
| 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.<sup>9</sup>

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.



## 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                                 |
| <b>I</b>                             | <b>B-R</b> | <b>In patients at increased risk, stage A HF, the optimal blood pressure in those with hypertension should be less than 130/80 mm Hg.<sup>189–193</sup></b>  | <b>NEW:</b> 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 <sup>191</sup> 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   |
| <b>I</b>   | <b>C-EO</b> | <b>Patients with HFrEF and hypertension should be prescribed GDMT titrated to attain systolic blood pressure less than 130 mm Hg.<sup>191</sup></b>   | <b>NEW:</b> 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   |
| <b>I</b>   | <b>C-LD</b> | <b>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.<sup>9,167,169,170,195–199</sup></b>   | <b>NEW:</b> 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. <sup>172</sup> 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   |
| <b>IIa</b>                                       | <b>C-LD</b> | <b>In patients with NYHA class II–IV HF and suspicion of sleep-disordered breathing or excessive daytime sleepiness, a formal sleep assessment is reasonable.<sup>200,201</sup></b>  | <b>NEW:</b> Recommendation reflects clinical necessity to distinguish obstructive versus central sleep apnea. |
| See Online Data Supplement G.                    |             | 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. <sup>202</sup> 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. <sup>203</sup> Continuous positive airway pressure (CPAP) for obstructive sleep apnea improves sleep quality, reduces the apnea-hypopnea index, and improves nocturnal oxygenation. <sup>200,201</sup>  |   |
| <b>IIb</b>                                       | <b>B-R</b>  | <b>In patients with cardiovascular disease and obstructive sleep apnea, CPAP may be reasonable to improve sleep quality and daytime sleepiness.<sup>204</sup></b>  | <b>NEW:</b> New data demonstrate the limited scope of benefit expected from CPAP for obstructive sleep apnea. |
| See Online Data Supplement G.                    |             | 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. <sup>204</sup> In this RCT of >2700 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. <sup>204</sup> 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 10132 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. <sup>205</sup> |   |

| Recommendations for Treatment of Sleep Disorders (Continued) |     |   |  |
|--|-----|---|--|
| COR  | LOE | Recommendations   | Comment/Rationale  |
| III: Harm  | B-R | In patients with NYHA class II–IV HFrEF and central sleep apnea, adaptive servo-ventilation causes harm. <sup>203</sup>   | <b>NEW:</b> New data demonstrate a signal of harm when adaptive servo-ventilation is used for central sleep apnea. |
| See Online Data Supplement G.                                |     | 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. <sup>203</sup> 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. |  |

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## FOOTNOTES

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**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                                     |
| Bykem 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  | <ul style="list-style-type: none"> <li>• Bayer†</li> <li>• Boehringer Ingelheim</li> <li>• CardioCell†</li> <li>• Luitpold</li> <li>• Medtronic</li> <li>• Merck†</li> <li>• Novartis†</li> <li>• Relypsat</li> <li>• Takeda</li> <li>• Trevena†</li> <li>• Z Pharma</li> <li>• Zensun</li> </ul> | • 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                              | <ul style="list-style-type: none"> <li>• Bayer†</li> <li>• Bayer (DSMB)</li> <li>• Novartis†</li> <li>• Servier Pharmaceuticals†</li> <li>• Vifor</li> </ul> | None  | None           | 7.3.2.10, 7.3.2.11, 7.3.3, 9.2, and 9.5. |
| Gregg C. Fonarow           | Ahmanson-UCLA Cardiomyopathy Center—Director; UCLA Division of Cardiology—Co-Chief   | <ul style="list-style-type: none"> <li>• Amgen</li> <li>• Janssen Pharmaceuticals</li> <li>• Novartis†</li> </ul>   | None            | None                              | • Novartis†  | None  | None           | 7.3.2.10, 7.3.2.11, 7.3.3, and 9.5.      |

(Continued)



## 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*                   |
|------------------------|---|--|-----------------|-----------------------------------|---|---|----------------|---|
| Michael M. Givertz     | Brigham and Women's Hospital—Professor of Medicine  | <ul style="list-style-type: none"> <li>Merck</li> <li>Novartis</li> </ul>  | 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                             | <ul style="list-style-type: none"> <li>Abbott</li> <li>Janssen Pharmaceuticals</li> <li>Novartis</li> <li>Relysat†</li> <li>ResMed†</li> </ul> | None            | None                              | <ul style="list-style-type: none"> <li>AstraZeneca</li> <li>Novartis†</li> </ul>                              | 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                              | <ul style="list-style-type: none"> <li>Novartis—PARENT trial (PI)</li> <li>NHLBI—INTERMACS (Co-PI)</li> </ul> | 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  $\geq 5\%$  of the voting stock or share of the business entity, or ownership of  $\geq \$5000$  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*<br>• Merck<br>• Novartis*<br>• Relypsa*<br>• St. Jude Medical* | None            | None                              | None   | • Novartis*<br>• 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<br>• AHA (GWTG Steering Committee)†<br>• 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 Raghuvier  | 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)<br>• GlaxoSmithKline (DSMB)<br>• NHLBI<br>• Otsuka | • Abbott Laboratories<br>• AHA*<br>• <i>Circulation/ Circulation: Heart Failure</i> †<br>• HFSA (Executive Council)†<br>• Pfizer/ GlaxoSmithKline<br>• 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<br>• Otsuka<br>• PCORI<br>• Thoratec   | None           |

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## Appendix 2. Continued

| Reviewer            | Representation  | Employment  | Consultant  | Speakers Bureau  | Ownership/ Partnership/ Principal | Personal Research   | Institutional, Organizational, or Other Financial Benefit   | Expert Witness |
|---------------------|---|---|---|--|-----------------------------------|---|---|----------------|
| David A. Baran      | Organizational Reviewer—ISHLT                                       | Newark Beth Israel Medical Center—Director of Heart Failure and Transplant Research   | <ul style="list-style-type: none"> <li>• Maquet</li> <li>• Otsuka*</li> </ul>   | <ul style="list-style-type: none"> <li>• Novartis</li> </ul> | None                              | <ul style="list-style-type: none"> <li>• XDx*</li> <li>• NIH*</li> </ul>  | None  | None           |
| Kenneth Casey       | Organizational Reviewer—CHEST                                       | Wm. S. Middleton Memorial Veterans Hospital—Director, Sleep Medicine  | None  | None   | None                              | None  | <ul style="list-style-type: none"> <li>• CHEST</li> </ul>   | 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  | <ul style="list-style-type: none"> <li>• ACC/AHA†</li> <li>• AHA†</li> <li>• ASA†</li> <li>• Catheterization and Cardiovascular Intervention†</li> <li>• NIH</li> <li>• Portland Metro Area AHA (President)†</li> <li>• SCAI Quality Interventional Council†</li> </ul> | 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 | <ul style="list-style-type: none"> <li>• Blue Cross/Blue Shield*</li> <li>• NQF†</li> <li>• Yale University</li> </ul>  | None   | None                              | <ul style="list-style-type: none"> <li>• Johns Hopkins (DSMB)</li> </ul>  | <ul style="list-style-type: none"> <li>• Association of University Anesthesiologists†</li> <li>• NIH</li> </ul>   | 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  | <ul style="list-style-type: none"> <li>• FH Foundation†</li> <li>• International FH Foundation†</li> </ul>  | None   | None                              | <ul style="list-style-type: none"> <li>• FH Foundation†</li> <li>• NIH*</li> </ul>  | None  | None           |
| James L. Januzzi    | Content Reviewer  | Massachusetts General Hospital—Hutter Family Professor of Medicine in the Field of Cardiology   | <ul style="list-style-type: none"> <li>• Critical Diagnostics*</li> <li>• Novartis*</li> <li>• Phillips</li> <li>• Roche Diagnostics*</li> <li>• Sphingotec*</li> </ul> | None   | None                              | <ul style="list-style-type: none"> <li>• Amgen (DSMB)</li> <li>• Boeringer Ingelheim (DSMB)*</li> <li>• Janssen Pharmaceuticals (DSMB)</li> <li>• Prevencio*</li> </ul> | 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           |

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## Appendix 2. Continued

| Reviewer               | Representation  | Employment  | Consultant  | Speakers Bureau | Ownership/ Partnership/ Principal | Personal Research   | Institutional, Organizational, or Other Financial Benefit  | Expert Witness |
|------------------------|---|---|---|-----------------|-----------------------------------|---|--|----------------|
| Wayne C. Levy          | Content Reviewer  | University of Washington—Professor of Medicine  | <ul style="list-style-type: none"> <li>Abbott Laboratories</li> <li>Biotronik</li> <li>GE Healthcare</li> <li>HeartWare</li> <li>PharminIN</li> </ul> | None            | None                              | <ul style="list-style-type: none"> <li>NIH</li> <li>Novartis*</li> <li>St. Jude Medical*</li> </ul>   | <ul style="list-style-type: none"> <li>Amgen*</li> <li>AHA</li> <li>HeartWare*</li> <li>Novartis*</li> <li>Resmed*</li> <li>Thoratec</li> </ul>          | None           |
| 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  | <ul style="list-style-type: none"> <li>Association of Black Cardiologists†</li> </ul>  | None           |
| Sean P. Pinney         | Content Reviewer—ACC Heart Failure and Transplant Council           | Mount Sinai School of Medicine—Associate Professor of Medicine, Cardiology  | <ul style="list-style-type: none"> <li>Acorda Therapeutics</li> <li>Thoratec</li> <li>XDx</li> </ul>  | None            | None                              | <ul style="list-style-type: none"> <li>Thoratec†</li> <li>NIH†</li> </ul>   | 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                                     | <ul style="list-style-type: none"> <li>BioControl</li> <li>Medtronic</li> <li>Novartis</li> </ul>   | None            | None                              | <ul style="list-style-type: none"> <li>Medtronic</li> <li>NIH*</li> <li>Novartis†</li> <li>St. Jude Medical†</li> </ul>   | <ul style="list-style-type: none"> <li>St. Jude Medical</li> </ul>   | None           |
| W.H. Wilson Tang       | Content Reviewer  | Cleveland Clinic Foundation—Assistant Professor of Medicine   | None  | None            | None                              | <ul style="list-style-type: none"> <li>NIH*</li> </ul>  | <ul style="list-style-type: none"> <li>Alnylam Pharmaceuticals</li> <li>NIH</li> <li>NHLBI</li> <li>Roche</li> <li>Novartis</li> <li>Thoratec</li> </ul> | None           |
| Emily J. Tsai          | Content Reviewer  | Columbia University College of Physicians & Surgeons—Assistant Professor of Medicine, Division of Cardiology  | None  | None            | None                              | <ul style="list-style-type: none"> <li>Bayert</li> <li>Bristol-Myers Squibb†</li> <li>NHLBI*</li> </ul>   | None   | None           |
| Duminda N. Wijesundera | 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                              | <ul style="list-style-type: none"> <li>CIHR (DSMB)†</li> <li>CIHR*</li> <li>Heart and Stroke Foundation of Canada*</li> <li>Ministry of Health &amp; Long-term Care of Ontario*</li> <li>PCORI (DSMB)†</li> </ul> | 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  $\geq 5\%$  of the voting stock or share of the business entity, or ownership of  $\geq \$5000$  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**

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|--|
| 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                      |