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ACC/AHA/HFSA FOCUSED UPDATE

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

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

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TABLE OF CONTENTS

PREAMBLE

Incorporation of new study results, medications, or devices that merit modification of existing clinical practice guideline recommendations, or the addition of new recommendations, is critical to ensuring that guidelines reflect current knowledge, available treatment options, and optimum medical care. To keep pace with evolving evidence, the American College of Cardiology (ACC)/American Heart Association (AHA) Task Force on Clinical Practice Guidelines ("Task Force") has issued this focused update to reassess guideline recommendations on the basis of recently published study data. This update has been subject to rigorous, multilevel review and approval, similar to the full guidelines. For specific focused update criteria and additional methodological details, please see the ACC/AHA guideline methodology manual (1).

Modernization

Processes have evolved over time in response to published reports from the Institute of Medicine (2,3) and ACC/AHA mandates (4-7), leading to adoption of a "knowledge byte" format. This process entails delineation of a recommendation addressing a specific clinical question, followed by concise text (ideally <250 words) and hyperlinked to supportive evidence. This approach better accommodates time constraints on busy clinicians, facilitates easier access to recommendations via electronic search engines and other evolving technology, and supports the evolution of guidelines as "living documents" that can be dynamically updated as needed.

Guideline-Directed Evaluation and Management

The term *guideline-directed evaluation and management* (GDEM) refers to care defined mainly by ACC/AHA Class I recommendations. For these and all recommended drug treatment regimens, the reader should confirm dosage with product insert material and carefully evaluate for contraindications and interactions. Recommendations are limited to treatments, drugs, and devices approved for clinical use in the United States.

Class of Recommendation and Level of Evidence

The Class of Recommendation (COR) and Level of Evidence (LOE) are derived independently of each other according to established criteria. The COR indicates the strength of recommendation, encompassing the estimated magnitude and certainty of benefit of a clinical action in proportion to risk. The LOE rates the quality of scientific evidence supporting the intervention on the basis of the type, quantity, and consistency of data from clinical trials and other sources (**Table 1**). Recommendations in this focused update reflect the new 2015 COR/LOE system, in which LOE B and C are subcategorized for the purpose of increased granularity (1,5,8).

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

CLASS I (STRONG) — **Benefit >>> Risk**

Suggested phrases for writing recommendations:
- Is recommended
- Is indicated/useful/effective/beneficial
- Should be performed/administered/other
- Comparative-Effectiveness Phrases†:
  - Treatment/strategy A is recommended/indicated in preference to treatment B
  - Treatment A should be chosen over treatment B

CLASS IIa (MODERATE) — **Benefit >> Risk**

Suggested phrases for writing recommendations:
- Is reasonable
- Can be useful/effective/beneficial
- 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

CLASS IIb (WEAK) — **Benefit ≥ Risk**

Suggested phrases for writing recommendations:
- 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

LEVEL (QUALITY) OF EVIDENCE‡

LEVEL A
- High-quality evidence‡ from more than 1 RCT
- Meta-analyses of high-quality RCTs
- One or more RCTs corroborated by high-quality registry studies

LEVEL B-R (Randomized)
- Moderate-quality evidence‡ from 1 or more RCTs
- Meta-analyses of moderate-quality RCTs

LEVEL B-NR (Nonrandomized)
- Moderate-quality evidence‡ from 1 or more well-designed, well-executed nonrandomized studies, observational studies, or registry studies
- Meta-analyses of such studies

LEVEL C-LD (Limited Data)
- 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

LEVEL C-EO (Expert Opinion)

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.

Relationships With Industry and Other Entities

The ACC and AHA exclusively sponsor the work of guideline writing committees without commercial support, and members volunteer time for this activity. Selected organizations and professional societies with related interests and expertise are invited to participate as partners or collaborators. The Task Force makes every effort to avoid actual, potential, or perceived conflicts of interest that might arise through relationships with industry or other entities (RWI). All writing committee members and reviewers are required to fully disclose current industry relationships or personal interests, beginning 12 months before initiation of the writing effort. Management of RWI involves selecting a balanced

writing committee and requires that both the chair and a majority of writing committee members have no relevant RWI (see Appendix 1 for the definition of *relevance*). Members are restricted with regard to writing or voting on sections to which RWI apply. Members of the writing committee who recused themselves from voting are indicated and specific section recusals are noted in Appendix 1. In addition, for transparency, members' comprehensive disclosure information is available as an Online Supplement, and reviewers' RWI disclosures are included in Appendix 2. Comprehensive disclosure information for the Task Force is also available online. The Task Force strives to avoid bias by selecting experts from a broad array of backgrounds representing different geographic regions, genders, ethnicities, intellectual perspectives, and scopes of clinical activities.

Intended Use

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 broader target. Although guidelines may be used to inform regulatory or payer decisions, the intent is to improve quality of care and align with patients' interests. The guidelines are reviewed annually by the Task Force and are official policy of the ACC and AHA. Each guideline is considered current unless and until it is updated, revised, or superseded by a published addendum.

Related Issues

For additional information pertaining to the methodology for grading evidence, assessment of benefit and harm, shared decision making between the patient and clinician, structure of evidence tables and summaries, standardized terminology for articulating recommendations, organizational involvement, peer review, and policies regarding periodic assessment and updating of guideline documents, we encourage readers to consult the ACC/AHA guideline methodology manual (1).

Jonathan L. Halperin, MD, FACC, FAHA
Chair, ACC/AHA Task Force on Clinical Practice Guidelines

INTRODUCTION

The ACC, the AHA, and the Heart Failure Society of America (HFSA) recognize that the introduction of effective new therapies that potentially affect a large number of patients presents both opportunities and challenges. The introduction of an angiotensin receptor-neprilysin inhibitor (ARNI) (valsartan/sacubitril) and a sinoatrial node modulator (ivabradine), when applied judiciously, complements established pharmacological and device-based therapies and represents a milestone in the evolution of care for patients with heart failure (HF). Accordingly, the writing committees of the "2016 ACC/AHA/HFSA Focused Update on New Pharmacological Therapy for Heart Failure" and the "2016 ESC Guideline on the Diagnosis and Treatment of Acute and Chronic Heart Failure" concurrently developed recommendations for the incorporation of these therapies into clinical practice. Working independently, each writing committee surveyed the evidence, arrived at similar conclusions, and constructed similar, but not identical, recommendations. Given the concordance, the respective organizations simultaneously issued aligned recommendations on the use of these new treatments to minimize confusion and improve the care of patients with HF.

Members of the ACC/AHA/HFSA writing committee without relevant RWI voted on the final recommendations. These were subjected to external peer review by 25 official, organizational, and content reviewers before approval by the Task Force and the leadership of the ACC, AHA, and HFSA, as well as endorsement by the American College of Chest Physicians and the International Society for Heart and Lung Transplantation. The statements issued by the European Society of Cardiology writing committee went through a similarly rigorous process of external review before endorsement by the societal leadership.

No single clinical trial answers all pertinent questions, nor can trial results be perfectly replicated in clinical practice. Several critical questions remain unanswered, and further experience in both ongoing trials and clinical therapeutics may require modification of these initial recommendations. On the basis of the currently available evidence, however, the recommendations that follow reflect our assessment of how best to proceed today.

7.3. STAGE C

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

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

See the *Online Data Supplement* for evidence supporting these recommendations.

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

COR	LOE	RECOMMENDATIONS
I	ACE: A ARB: A ARNI: B-R	**The clinical strategy of inhibition of the renin-angiotensin system with ACE inhibitors *(Level of Evidence: A)* (9–14), OR ARBs *(Level of Evidence: A)* (15–18), OR ARNI *(Level of Evidence: B-R)* (19) in conjunction with evidence-based beta blockers (20–22), and aldosterone antagonists in selected patients (23,24), is recommended for patients with chronic HF*r*EF to reduce morbidity and mortality.**

See Online Data Supplements 1, 2, 18–20.

Angiotensin-converting enzyme (ACE) inhibitors reduce morbidity and mortality in heart failure with reduced ejection fraction (HF*r*EF). 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 (9–14). 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 (15–18) 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 HF*r*EF 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% (19). 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: A	**The use of ACE inhibitors is beneficial for patients with prior or current symptoms of chronic HF*r*EF to reduce morbidity and mortality (9–14,25).**

See Online Data Supplement 18.

ACE inhibitors have been shown in large RCTs to reduce morbidity and mortality in patients with HF*r*EF with mild, moderate, or severe symptoms of HF, with or without coronary artery disease (9–14). Data suggest that there are no differences among available ACE inhibitors in their effects on symptoms or survival (25). 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 (26). 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 HF*r*EF has been found to be superior, *for those patients for whom ARNI is not appropriate, continued use of an ACE inhibitor for all classes of HF*r*EF remains strongly advised.*

I	ARB: A	**The use of ARBs to reduce morbidity and mortality is recommended in patients with prior or current symptoms of chronic HF*r*EF who are intolerant to ACE inhibitors because of cough or angioedema (15–18,27,28).**

See Online Data Supplements 2 and 19.

ARBs have been shown to reduce mortality and HF hospitalizations in patients with HF*r*EF in large RCTs (15–18). Long-term therapy with ARBs in patients with HF*r*EF produces hemodynamic, neurohormonal, and clinical effects consistent with those expected after interference with the renin-angiotensin system (27,28). 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. *For those patients for whom an ACE inhibitor or ARNI is inappropriate, use of an ARB remains advised.*

I	ARNI: B-R	**In patients with chronic symptomatic HF*r*EF NYHA class II or III who tolerate an ACE inhibitor or ARB, replacement by an ARNI is recommended to further reduce morbidity and mortality (19).**
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 (10). This ARNI has recently been approved for patients with symptomatic HF*r*EF 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 (29). 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 (30).
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 (31,32).**
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 (31,32) 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 (32,33). An ARNI should not be administered within 36 hours of switching from or to an ACE inhibitor.
III: Harm	C-EO	**ARNI should not be administered to patients with a history of angioedema.**
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 HF*r*EF (31). In a very large RCT of hypertensive patients, ompatrilat was associated with a 3-fold increased risk of angioedema as compared with enalapril (32). Blacks and smokers were particularly at risk. The high incidence of angioedema ultimately led to cessation of the clinical development of omapatrilat (34,35). In light of these observations, angioedema was an exclusion criterion in the first large trial assessing ARNI therapy in patients with hypertension (36) and then in the large trial that demonstrated clinical benefit of ARNI therapy in HF*r*EF (19). 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

See the *Online Data Supplement* for evidence supporting this recommendation.

Recommendation for Ivabradine

COR	LOE	RECOMMENDATION
IIa	B-R	**Ivabradine can be beneficial to reduce HF hospitalization for patients with symptomatic (NYHA class II-III) stable chronic HF*r*EF (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 (37–40).**

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 (38). The benefit of ivabradine was driven by a reduction in HF hospitalization. The study included patients with HF*r*EF (New York Heart Association [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 bpm. 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 (20–22,38). 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 (38).

The remainder of the "2016 ACC/AHA/HFSA Focused Update on the Management of Heart Failure: An Update of the 2013 ACCF/AHA Guideline for the Management of Heart Failure" will be forthcoming.

PRESIDENTS AND STAFF

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KEY WORDS ACC/AHA Clinical Practice Guidelines, angioedema, angiotensin-converting enzyme inhibitors, angiotensin receptor blockers, angiotensin receptor-neprilysin inhibitor, beta blockers, focused update, heart failure, ivabradine, natriuretic peptides

APPENDIX 1. AUTHOR RELATIONSHIPS WITH INDUSTRY AND OTHER ENTITIES (RELEVANT)—2016 ACC/AHA/HFSA FOCUSED UPDATE ON NEW PHARMACOLOGICAL THERAPY FOR 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	University of Pennsylvania—Professor of Medicine	None	None	None	None	None	None	None
Biykem Bozkurt	Michael E. DeBakey VA Medical Center—The Mary and Gordon Cain Chair and Professor of Medicine	None	None	None	■ Novartis	None	None	7.3.2.10 and 7.3.2.11.
Javed Butler	Stony Brook University—Division Chief of Cardiology	■ Bayer† ■ CardioCell† ■ Medtronic ■ Merck† ■ Novartis† ■ Relypsa† ■ Takeda ■ Trevena† ■ Z Pharma ■ Zensun	■ Novartis†	None	■ Amgen (DSMB)†	None	None	7.3.2.10 and 7.3.2.11.
Donald E. Casey, Jr	Thomas Jefferson College of Population Health—Adjunct 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	■ Trevena†	None	■ DCRI/Otsuka ■ UptoDate	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 and 7.3.2.11.
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 and 7.3.2.11.
Michael M. Givertz	Brigham and Women's Hospital—Professor of Medicine	■ Merck ■ Novartis	None	None	None	None	None	7.3.2.10 and 7.3.2.11.

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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*
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	7.3.2.10 and 7.3.2.11.
Frederick A. Masoudi	University of Colorado, Denver—Associate Professor of Medicine, Division of Cardiology	None	None	None	None	None	None	None
Patrick E. McBride	University of Wisconsin School of Medicine and Public Health—Professor of Medicine and Family Medicine; Associate 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 W. 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 and 7.3.2.11.
Cheryl Westlake	Azusa Pacific University—Professor and Associate Dean, International and Community Programs	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; AHA, American Heart Association; DCRI, Duke Clinical Research Institute; DSMB, data safety monitoring board; HFSA, Heart Failure Society of America; INTERMACS, The Interagency Registry for Mechanically Assisted Circulatory Support; NHLBI, National Heart, Lung, and Blood Institute; 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)—2016 ACC/AHA/HFSA FOCUSED UPDATE ON NEW PHARMACOLOGICAL THERAPY FOR HEART FAILURE (MARCH 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; Harvard Medical School, Associate Professor of Medicine	■ 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—Associate 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	■ Relypsa	None	None	None	None	None
Geetha Raghuveer	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 (Eligibility Committee) ■ AHA* ■ Circulation/Circulation: Heart Failure† ■ HFSA (Executive Council)† ■ Pfizer/GlaxoSmithKline (Clinical Events Committee) ■ Sunshine Heart (Eligibility Committee)	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	■ CareDX-IMAGE trial (Steering Committee)* ■ NIH*	None	None

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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

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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 ■ CareDX	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, Section of Cardiology	None	None	None	■ Bayer† ■ Bristol-Myers Squib† ■ NHLBI*	None	None
Duminda N. Wijeysundera	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

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*Significant relationship.

†No financial benefit.

AAFP indicates American Academy of Family Physicians; ACC, American College of Cardiology; 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; IMAGE, Invasive Monitoring Attenuation through Gene Expression; 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 Cardiovascular Angiography and Interventions; SUNY, State University of New York; UT, University of Texas; and VA, Veterans Affairs.