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 International Society for Heart and Lung Transplantation

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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).

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 (http://circ.ahajournals.org/lookup/suppl/doi:10.1161/CIR.0000000000000435/-/DC1), and reviewers' RWI disclosures are included in Appendix 2. Comprehensive disclosure information for the Task Force is also available at http://www.acc.org/about-acc/leadership/guidelines-and-documents-task-forces.aspx 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 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.

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.

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* (http://circ.ahajournals.org/lookup/suppl/doi:10.1161/CIR.0000000000000435/-/DC2) for evidence supporting these recommendations.

<table>
<tr><th colspan="3">Recommendations for Renin-Angiotensin System Inhibition With ACE Inhibitor or ARB or ARNI</th></tr>
<tr><th>COR</th><th>LOE</th><th>Recommendations</th></tr>
<tr><td rowspan="3">I</td><td>ACE: A</td><td rowspan="3">The clinical strategy of inhibition of the renin-angiotensin system with ACE inhibitors (Level of Evidence: A) (9-14), <u>OR</u> ARBs (Level of Evidence: A) (15-18), <u>OR</u> 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 HFrEF to reduce morbidity and mortality.</td></tr>
<tr><td>ARB: A</td></tr>
<tr><td>ARNI: B-R</td></tr>
<tr><td>See Online Data Supplements 1, 2, 18-20.</td><td colspan="2">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 (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,</td></tr>
</table>

		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 HFrEF 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* (http://circ.ahajournals.org/lookup/suppl/doi:10.1161/CIR.0000000000000435/-/DC2) 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 (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 (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.

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References

1. ACCF/AHA Task Force on Practice Guidelines. Methodology Manual and Policies From the ACCF/AHA Task Force on Practice Guidelines. Available at: http://assets.cardiosource.com/Methodology_Manual_for_ACC_AHA_Writing_Committees.pdf and http://my.americanheart.org/idc/groups/ahamah-public/@wcm/@sop/documents/downloadable/ucm_319826.pdf. 2010; American College of Cardiology and American Heart Association. Accessed April 7, 2016.
2. Committee on Standards for Developing Trustworthy Clinical Practice Guidelines, Institute of Medicine (U.S.). *Clinical Practice Guidelines We Can Trust*. Washington, DC: National Academies Press; 2011.
3. Committee on Standards for Systematic Reviews of Comparative Effectiveness Research, Institute of Medicine (U.S.). *Finding What Works in Health Care: Standards for Systematic Reviews*. Washington, DC: National Academies Press; 2011.
4. Jacobs AK, Kushner FG, Ettinger SM, et al. ACCF/AHA clinical practice guideline methodology summit report: a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines. Circulation. 2013;127:268-310.
5. Jacobs AK, Anderson JL, Halperin JL. The evolution and future of ACC/AHA clinical practice guidelines: a 30-year journey: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines. Circulation. 2014;130:1208–17.
6. Anderson JL, Heidenreich PA, Barnett PG, et al. ACC/AHA statement on cost/value methodology in clinical practice guidelines and performance measures: a report of the American College of Cardiology/American Heart Association Task Force on Performance Measures and Task Force on Practice Guidelines. Circulation. 2014;129:2329–45.
7. Arnett DK, Goodman RA, Halperin JL, et al. AHA/ACC/HHS strategies to enhance application of clinical practice guidelines in patients with cardiovascular disease and comorbid conditions: from the American Heart Association, American College of Cardiology, and U.S. Department of Health and Human Services. Circulation. 2014;130:1662–7.
8. Halperin JL, Levine GN, Al-Khatib SM, et al. Further evolution of the ACC/AHA clinical practice guideline recommendation classification system: a report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines. Circulation. 2016;133:1426-28.
9. Effects of enalapril on mortality in severe congestive heart failure. Results of the Cooperative North Scandinavian Enalapril Survival Study (CONSENSUS). The CONSENSUS Trial Study Group. N Engl J Med. 1987;316:1429-35.
10. Effect of enalapril on survival in patients with reduced left ventricular ejection fractions and congestive heart failure. The SOLVD Investigators. N Engl J Med. 1991;325:293-302.
11. Packer M, Poole-Wilson PA, Armstrong PW, et al. Comparative effects of low and high doses of the angiotensin-converting enzyme inhibitor, lisinopril, on morbidity and mortality in chronic heart failure. ATLAS Study Group. Circulation. 1999;100:2312-8.
12. Pfeffer MA, Braunwald E, Moye LA, et al. Effect of captopril on mortality and morbidity in patients with left ventricular dysfunction after myocardial infarction. Results of the survival and ventricular enlargement trial. The SAVE Investigators. N Engl J Med. 1992;327:669-77.
13. Effect of ramipril on mortality and morbidity of survivors of acute myocardial infarction with clinical evidence of heart failure. The Acute Infarction Ramipril Efficacy (AIRE) Study Investigators. Lancet. 1993;342:821-8.
14. Køber L, Torp-Pedersen C, Carlsen JE, et al. A clinical trial of the angiotensin-converting-enzyme inhibitor trandolapril in patients with left ventricular dysfunction after myocardial infarction. Trandolapril Cardiac Evaluation (TRACE) Study Group. N Engl J Med. 1995;333:1670-6.
15. Cohn JN, Tognoni G, Valsartan Heart Failure Trial Investigators. A randomized trial of the angiotensin-receptor blocker valsartan in chronic heart failure. N Engl J Med. 2001;345:1667-75.
16. Pfeffer MA, McMurray JJV, Velazquez EJ, et al. Valsartan, captopril, or both in myocardial infarction complicated by heart failure, left ventricular dysfunction, or both. N Engl J Med. 2003;349:1893-906.
17. Konstam MA, Neaton JD, Dickstein K, et al. Effects of high-dose versus low-dose losartan on clinical outcomes in patients with heart failure (HEAAL study): a randomised, double-blind trial. Lancet. 2009;374:1840-8.

18. Pfeffer MA, Swedberg K, Granger CB, et al. Effects of candesartan on mortality and morbidity in patients with chronic heart failure: the CHARM-Overall programme. Lancet. 2003;362:759-66.
19. McMurray JJV, Packer M, Desai AS, et al. Angiotensin-neprilysin inhibition versus enalapril in heart failure. N Engl J Med. 2014;371:993-1004.
20. Effect of metoprolol CR/XL in chronic heart failure: Metoprolol CR/XL Randomised Intervention Trial in Congestive Heart Failure (MERIT-HF). Lancet. 1999;353:2001-7.
21. Packer M, Fowler MB, Roecker EB, et al. Effect of carvedilol on the morbidity of patients with severe chronic heart failure: results of the carvedilol prospective randomized cumulative survival (COPERNICUS) study. Circulation. 2002;106:2194-9.
22. Yancy CW, Jessup M, Bozkurt B, et al. 2013 ACCF/AHA guideline for the management of heart failure: a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines. Circulation. 2013;128:e240–327.
23. Eschalier R, McMurray JJV, Swedberg K, et al. Safety and efficacy of eplerenone in patients at high risk for hyperkalemia and/or worsening renal function: analyses of the EMPHASIS-HF study subgroups (Eplerenone in Mild Patients Hospitalization And SurvIval Study in Heart Failure). J Am Coll Cardiol. 2013;62:1585-93.
24. Pitt B, Zannad F, Remme WJ, et al. The effect of spironolactone on morbidity and mortality in patients with severe heart failure. Randomized Aldactone Evaluation Study Investigators. N Engl J Med. 1999;341:709-17.
25. Garg R, Yusuf S. Overview of randomized trials of angiotensin-converting enzyme inhibitors on mortality and morbidity in patients with heart failure. Collaborative Group on ACE Inhibitor Trials. JAMA. 1995;273:1450-6.
26. Woodard-Grice AV, Lucisano AC, Byrd JB, et al. Sex-dependent and race-dependent association of XPNPEP2 C-2399A polymorphism with angiotensin-converting enzyme inhibitor-associated angioedema. Pharmacogenet Genomics. 2010;20:532-6.
27. Yusuf S, Teo KK, Pogue J, et al. Telmisartan, ramipril, or both in patients at high risk for vascular events. ONTARGET Investigators. N Engl J Med. 2008;358:1547-59.
28. Yusuf S, Teo K, Anderson C, et al. Effects of the angiotensin-receptor blocker telmisartan on cardiovascular events in high-risk patients intolerant to angiotensin-converting enzyme inhibitors: a randomised controlled trial. Telmisartan Randomised AssessmeNt Study in ACE iNtolerant subjects with cardiovascular Disease (TRANSCEND) Investigators. Lancet. 2008;372:1174-83.
29. Entresto [package insert]. Hanover, NJ: Novartis Pharmaceuticals Corporation; 2015.
30. Solomon SD, Zile M, Pieske B, et al. The angiotensin receptor neprilysin inhibitor LCZ696 in heart failure with preserved ejection fraction: a phase 2 double-blind randomised controlled trial. Lancet. 2012;380:1387-95.
31. Packer M, Califf RM, Konstam MA, et al. Comparison of omapatrilat and enalapril in patients with chronic heart failure: the Omapatrilat Versus Enalapril Randomized Trial of Utility in Reducing Events (OVERTURE). Circulation. 2002;106:920-6.
32. Kostis JB, Packer M, Black HR, et al. Omapatrilat and enalapril in patients with hypertension: the Omapatrilat Cardiovascular Treatment vs. Enalapril (OCTAVE) trial. Am J Hypertens. 2004;17:103-11.
33. Vardeny O, Miller R, Solomon SD. Combined neprilysin and renin-angiotensin system inhibition for the treatment of heart failure. JACC Heart Fail. 2014;2:663-70.
34. Messerli FH, Nussberger J. Vasopeptidase inhibition and angio-oedema. Lancet. 2000;356:608-9.
35. Braunwald E. The path to an angiotensin receptor antagonist-neprilysin inhibitor in the treatment of heart failure. J Am Coll Cardiol. 2015;65:1029-41.
36. Ruilope LM, Dukat A, Böhm M, et al. Blood-pressure reduction with LCZ696, a novel dual-acting inhibitor of the angiotensin II receptor and neprilysin: a randomised, double-blind, placebo-controlled, active comparator study. Lancet. 2010;375:1255-66.
37. Böhm M, Robertson M, Ford I, et al. Influence of Cardiovascular and Noncardiovascular Co-morbidities on Outcomes and Treatment Effect of Heart Rate Reduction With Ivabradine in Stable Heart Failure (from the SHIFT Trial). Am J Cardiol. 2015;116:1890-7.
38. Swedberg K, Komajda M, Böhm M, et al. Ivabradine and outcomes in chronic heart failure (SHIFT): a randomised placebo-controlled study. Lancet. 2010;376:875-85.
39. Fox K, Ford I, Steg PG, et al. Ivabradine in stable coronary artery disease without clinical heart failure. N Engl J Med. 2014;371:1091-9.

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

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

Committee Member	Employment	Consultant	Speakers Bureau	Ownership/ Partnership / Principal	Personal Research	Institutional, Organizational, or Other Financial Benefit	Expert Witness	Voting Recusals By Section*
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.
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

Committee Member	Employment	Consultant	Speakers Bureau	Ownership/ Partnership / Principal	Personal Research	Institutional, Organizational, or Other Financial Benefit	Expert Witness	Voting Recusals By Section*
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; 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; Associate Professor of Medicine, Harvard Medical School	• Medscape Cardiology* • Merck • Novartis* • Relypsa* • St. Jude Medical*	None	None	None	• Novartis* • Thoratec	None
Anita Deswal	Official Reviewer—AHA	Michael E. DeBakey VA Medical Center—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	• Relypsa	None	None	None	None	None

		for Academic Affairs, Cardiology						
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	• XDx–IMAGE trial (Steering Committee)* • NIH*	None	None
Kenneth Casey	Organizational Reviewer—CHEST	Wm. S. Middleton Memorial Veterans Hospital—Director, Sleep Medicine	None	None	None	None	• ACCP	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	None	None	• Amgen (DSMB) • Boeringer Ingelheim (DSMB)* • Janssen	None	None

			Diagnostics* • Sphingotec*			Pharmaceuticals (DSMB) • Prevencio*		
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
Judith E. Mitchell	Content Reviewer	SUNY Downstate Medical Center—Director/Heart Failure Center; SUNY Downstate College of Medicine—Associate Professor of Medicine	None	None	None	None	• Association of Black Cardiologists†	None
Sean P. Pinney	Content Reviewer—ACC Heart Failure and Transplant Council	Mount Sinai School of Medicine—Associate Professor of Medicine, Cardiology	• Acorda Therapeutics • Thoratec • XDx	None	None	• Thoratec† • NIH†	None	None
Randall C. Starling	Content Reviewer—ACC Heart Failure and Transplant Council	Cleveland Clinic Department of Cardiovascular Medicine—Vice Chairman, Department of Cardiovascular Medicine; Section Head, Heart Failure & Cardiac Transplant	• BioControl • Medtronic • Novartis	None	None	• Medtronic • NIH* • Novartis† • St. Jude Medical†	• St. Jude Medical	None

W. H. Wilson Tang	Content Reviewer	Cleveland Clinic Foundation—Assistant Professor of Medicine	None	None	None	• NIH*	• Alnylam Pharmaceuticals • NIH • NHLBI • Roche • Novartis • Thoratec	None
Emily J. Tsai	Content Reviewer	Columbia University College of Physicians & Surgeons—Assistant Professor, 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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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; 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.

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Clyde W. Yancy, Mariell Jessup, Biykem Bozkurt, Javed Butler, Donald E. Casey, Jr, Monica M. Colvin, Mark H. Drazner, Gerasimos Filippatos, Gregg C. Fonarow, Michael M. Givertz, Steven M. Hollenberg, JoAnn Lindenfeld, Frederick A. Masoudi, Patrick E. McBride, Pamela N. Peterson, Lynne Warner Stevenson and Cheryl Westlake

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Committee Member	Employment	Consultant	Speakers Bureau	Ownership/ Partnership/ Principal	Personal Research	Institutional, Organizational or Other Financial Benefit	Expert Witness
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	• PCORI†	• JAMA Cardiology (Deputy Editor)*	None
Mariell Jessup *(Vice Chair)*	University of Pennsylvania—Professor of Medicine	None	None	None	None	• ABIM† • AHA† • Up to Date	None
Biykem Bozkurt	Michael E. DeBakey VA Medical Center—The Mary and Gordon Cain Chair and Professor of Medicine	None	None	None	• Novartis†	• ABIM	None
Javed Butler	Stony Brook University—Division Chief of Cardiology	• Bayer* • Boehringer Ingelheim* • CardioCell* • Janssen Pharmaceuticals • Medscape • Medtronic • Merck* • Novartis* • PharmaIn • Relypsa* • Stealth Peptide • Takeda† • Trevena* • Z Pharma • Zensun	• Novartis*	None	• Amgen (DSMB)* • Corvia Medical (DSMB) • European Union* • NIH*	• AHA (Deputy Chief Science Officer)* • American Heart Journal (Editorial Board)† • European Journal of Heart Failure (Associate Editor)† • HFSA (Executive Council Member)† • JACC† • JACC: Heart Failure† • NIH • St. Jude Medical	None
Donald E. Casey, Jr	Thomas Jefferson College of Population Health—Adjunct Faculty; Alvarez & Marsal IPO4Health—Principal and	None	None	None	None	None	None

	Founder						
Monica M. Colvin	University of Michigan—Associate Professor of Medicine, Cardiology	None	None	None	• Scientific Registry of Transplant Recipients/HRSA*	• CareDX • Thoratec	None
Mark H. Drazner	University of Texas Southwestern Medical Center—Professor, Internal Medicine	None	None	• Trevena*	• AHA*	• Alnylam • DCRI/Otsuka • AHA Circulation (Senior Associate Editor)† • NHLBI–GUIDE-IT (Co–PI) • St. Jude Medical (HF Fellowship)* • Up to Date	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 (Steering Committee)* • Bayer (DSMB) • Cardiorentis (Steering Committee)† • European Union* • Medtronic (Steering Committee)† • Novartis (Steering Committee)* • Servier Pharmaceuticals (Steering Committee)* • Vifor (Endpoint Adjudication Committee)	• European Heart Journal (Associate Editor)	None
Gregg C. Fonarow	Ahmanson-UCLA Cardiomyopathy Center—Director; UCLA Division of Cardiology—Co-Chief	• Amgen • Janssen Pharmaceuticals • Medtronic • Novartis*	None	None	• Medtronic–IMPROVE-HF (Steering Committee)† • NHLBI* • NIH/NIAID* • Novartis*	• ACC/AHA Task Force on Data Standards† • ACC/AHA Task Force on Performance Measures (Chair-Elect)† • ACTION Registry GWTG Steering Committee (Chair)† • AHA Consumer Health	None

						Quality Coordinating Committee† • AHA Manuscript Oversight Committee† • GWTG Steering Committee (PRT)† • JAMA Cardiology (Associate Editor)†	
Michael M. Givertz	Brigham and Women's Hospital—Professor of Medicine	• Cardioxyl • Merck • Novartis	None	None	• BioControl (Clinical Events Committee)	None	None
Steven M. Hollenberg	Cooper University Hospital—Director, Coronary Care Unit, Professor of Medicine	None	None	None	None	None	None
JoAnn Lindenfeld	Vanderbilt Heart and Vascular Institute—Director, Advanced Heart Failure and Transplant Section—Professor of Medicine	• Abbott • Boston Scientific • Cardiomems* • CVRx • Janssen Pharmaceuticals • Novartis • Relypsa* • RESMED*	None	None	• AstraZeneca† • Novartis* • St. Jude Medical*	• JACC HF (Deputy Editor)	None
Frederick A. Masoudi	University of Colorado, Denver—Associate Professor of Medicine, Division of Cardiology	• ABIM	None	None	• ACC* • ACC-NCDR* • AHRQ*	• Circulation (Associate Editor) • JournalWatch Cardiology (Associate Editor)	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	• NIH-NIDDK (DSMB)	None	None
Pamela N. Peterson	University of Colorado, Denver Health Medical Center—Associate Professor	• ACC*	None	None	None	• JAHA (Associate Editor)*	None

	of Medicine, Division of Cardiology						
Lynne W. Stevenson	Brigham and Women's Hospital Cardiovascular Division—Director, Cardiomyopathy and Heart Failure Program	• St. Jude Medical	None	None	• Novartis—PARENT (PI) • NHLBI • NHLBI—INTERMACS (Co–PI)† • St. Jude Medical	• Circulation Heart Failure (Senior Associate Editor)†	None
Cheryl Westlake	Azusa Pacific University—Professor and Associate Dean, International and Community Programs	None	None	None	None	None	None

This table represents all relationships of committee members with industry and other entities that were reported by authors, including those not deemed to be relevant to this document, at the time this document was under development. 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. Please refer to http://www.acc.org/guidelines/about-guidelines-and-clinical-documents/relationships-with-industry-policy for definitions of disclosure categories or additional information about the ACC/AHA Disclosure Policy for Writing Committees.

*Significant relationship.
†No financial benefit.

ACC indicates American College of Cardiology; AHA, American Heart Association; ABIM, American Board of Internal Medicine; AHRQ, Agency for Healthcare Research and Quality; DCRI, Duke Clinical Research Institute; DSMB, data safety monitoring board; GWTG, Get With The Guidelines; HF, heart failure; HFSA, Heart Failure Society of America; HRSA, Heath Resources and Services Administration; HSAG, Health Services Advisory Group; IMPROVE-HF, Registry to Improve the Use of Evidence-Based Heart Failure Therapies in the Outpatient Setting; INTERMACS, Interagency Registry for Mechanically Assisted Circulatory Support; JAHA, Journal of the American Heart Association; PCORI, Patient-Centered Outcomes Research Institute; PI, principal investigator; PRT, pharmaceutical round table; NIDDK, National Institute of Diabetes and Digestive and Kidney Diseases; NIH, National Institutes of Health; NHLBI, National Heart, Lung, and Blood Institute; NIAID, National Institute of Allergy and Infectious Diseases; UCLA, University of California, Los Angeles; and VA, Veterans Affairs.

2016 ACC/AHA/HFSA Focused Update on New Pharmacological Therapy for Heart Failure Data Supplement

(Section numbers correspond to the 2013 full-text guideline.)

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Data Supplement 1. RCTs Comparing ARNI (Section 7.3.2.10)

Study Acronym; Author; Year Published	Aim of Study; Study Type; Study Size (N)	Patient Population	Study Intervention (# patients) / Study Comparator (# patients)	Endpoint Results (Absolute Event Rates, P values; OR or RR; & 95% CI)	Relevant 2° Endpoint (if any); Study Limitations; Adverse Events
PARAMOUNT Solomon et al. 2012 (1) 22932717	Aim: To address safety and efficacy of LCZ696 (ARNI) in pts with HF*p*EF Study type: RCT Size: 308	Inclusion criteria: Pts ≥40 y of age, LVEF ≥45%, NYHA class II-III HF, NT-pro BNP >400 pg/mL. Exclusion criteria: Right HF due to pulmonary disease, dyspnea due to noncardiac causes, valvular/myocardial disease, CAD or CVD needing revascularization within 3 mo of screening.	Intervention: LCZ696 (149) target dose 200 mg BID achieved in 81% Comparator: Valsartan (152) target dose 160 mg BID achieved in 78%	1° endpoint: • Change from BL at 12 wk for NT-proBNP • Results: Reduction in LCZ696 group vs. valsartan (ratio of change from BL: 0.77, 95% CI: 0.64–0.92; p=0.005) 1° Safety endpoint: • LCZ-696 well tolerated. • Serious adverse events:	• No difference in change in NT-proBNP from BL at 36 wk • BP reduced in the LCZ696 group vs. valsartan at 12 wk (p=0.001 for SBP and p=0.09 for DBP) • Change in BP correlated poorly with the change in pro-BNP • No difference in improvement in NYHA class at 12 wk (p=0.11) and 36 wk (p=0.05). • No difference in KCCQ scores • Trial not powered to ascertain clinical

				15% in LCZ696 vs. 20% in valsartan group	outcomes. Further studies needed to assess safety and efficacy in HF*p*EF pts.
PARADIGM-HF McMurray et al. 2014 (2) 25176015	Aim: To compare survival rates with the use of LCZ696 with enalapril in HF Study type: RCT Size: 8,442	Inclusion criteria: ≥18 y of age, NYHA class II, III, IV; EF ≤35%, BNP of at least 150 pg/mL, hospitalized for HF ≤12 mo (≥BNP100 pg/mL), on ACE inhibitors or ARBs ≥4 wk before screening, required to take stable dose of beta blockers and an ACE inhibitor (or ARB) equal to 10mg of enalapril. Prior to randomization pts were required to complete 2 wk each of enalapril 10 mg BID and LCZ 100 BID. Exclusion criteria: Symptomatic hypotension, SBP <95 mm Hg, eGFR <30 mL/min/min/1.73m^2 of body surface area, serum K level >5.2 mmol/L, angioedema history, unacceptable side effects of ACE inhibitors or ARBs	Intervention: LCZ696 (4,187) target dose 200 mg BID (mean 375±71 mg daily) Comparator: Enalapril (4,212) target 10 mg BID (mean 18.9±3.4 mg daily)	1° endpoint: • Composite of death (CV causes) or a first hospitalization for HF • Results: Composite less in LCZ696 group vs. enalapril, 914 (21.8%) vs. 1,117, (26.5%) HR: 0.80 (95% CI: 0.73–0.87; p<0.001)	• Less CV death in LCZ696 arm (558 vs. 693) HR: 0.8 (95% CI: 0.71–0.89; p<0.001) • Less HF hospitalizations in LCZ696 arm (537 vs. 658) HR: 0.79 (95% CI: 0.71–0.89; p<0.001) • Less death from any cause in LCZ696 arm (711 vs. 835), HR: 0.84 (95% CI: 0.76–0.93; p<0.001) • The change from baseline to 8 mo in the score on the KCCQ in LCZ696 arm (2.99 points reduction vs. 4.63 points), HR: 1.64 (95% CI: 0.63–2.65; p=0.001) • No difference in new onset of AF (84 vs. 83; p=0.84) • No difference in protocol defined decline in renal function, HR: 0.86 (95% CI: 0.65–1.13; p=0.28). • More symptomatic hypotension (14% vs. 9.2%; p<0.001) • No difference in angioedema, 19 vs.10 (p=0.13)

AF indicates atrial fibrillation; ARNI/LCZ696, angiotensin receptor-neprilysin inhibitor; ACE, angiotensin-converting enzyme; ARB, angiotensin-receptor blocker; BL, baseline; BID; twice a day; BNP, plasma B-type natriuretic peptide; BP, blood pressure; CAD, coronary artery disease; CI, confidence interval; CVD, cardiovascular disease; CV, cardiovascular; EF, ejection fraction; eGFR, estimated glomerular filtration rate; HF, heart failure; HF*p*EF, heart failure with preserved ejection fraction; HR, hazard ratio; KCCQ, Kansas City Cardiomyopathy Questionnaire; LVEF, left ventricular ejection fraction; N/A, not available; NT-proBNP, N-terminal pro-B-type natriuretic peptide; NYHA, New York Heart Association; PARAMOUNT, Prospective Comparison of ARNI With ARB on Management of Heart Failure With Preserved Ejection Fraction; PARADIGM-HF, Prospective Comparison of ARNI With ACE to Determine Impact on Global Mortality and Morbidity in Heart Failure; pts, patients; RCT, randomized controlled trial; and SBP, systolic blood pressure.

Search Terms and Date: 3 trials identified by chairs in December 2015.

Data Supplement 2. RCTs Comparing RAAS Inhibition (Section 7.3.2.3)

Study Acronym; Author; Year Published	Aim of Study; Study Type; Study Size (N)	Patient Population	Study Intervention (# patients) / Study Comparator (# patients)	Endpoint Results (Absolute Event Rates, P values; OR or RR; & 95% CI)	Relevant 2° Endpoint (if any); Study Limitations; Adverse Events
ONTARGET ONTARGET Investigators et al. 2008 (3) 18378520	Aim: Compare ACE (ramipril), ARB (telmisartan), and combination ACE/ARB in pts with CVD or high-risk DM Study Type: RCT Size: 25,620	Inclusion Criteria: Pts >55 y of age, CAD, PVD, previous stroke, or high-risk DM with end-organ damage Exclusion Criteria: HF at trial entry, ACE or ARB intolerance, revascularization planned or <3 mo	Intervention: Runin, then randomization to ramipril (8,576) target dose 10 mg daily, telmisartan (8,542) target dose 80 mg daily or combination (8,502), titrated to BP	1° endpoint: • Composite of CV death, MI, stroke, or HF hospitalization at 5 y Results: No difference in outcome (16.5% ACE, 16.7% ARB, 16.3% combination; CI: ARB RR: 1.01 (95% CI: 0.94–1.09)	• Compared to the ramipril arm: • Telmisartan had more hypotensive symptoms (p<0.001); less cough (p<0.001) and angioedema (p=0.01); same syncope. • Combination arm had more hypotensive symptoms (p<0.001); syncope (p=0.03); and renal dysfunction (p<0.001) • BP fell by 6.4/7.4/9.8 mm Hg • Less angioedema with telmisartan
TRANSCEND Yusuf et al. 2008 (4) 18757085	Aim: To assess the effectiveness of ARB in ACE-intolerant pts with CVD or high-risk DM Study Type: RCT Size: 5,926	Inclusion Criteria: ACE-intolerant pts with CAD, PVD, previous stroke, or high-risk DM with end-organ damage Exclusion Criteria: HF at trial entry, revascularization planned or <3 mo	Intervention: Run in, then randomization to telmisartan titrated to 80 mg as tolerated (2,954) Comparator: Titration of other mediations as needed to control BP (2,944)	1° endpoint: • Composite of CV death, MI, stroke, or HF hospitalization at 5 y Results: No significant difference RR: 0.92 (95% CI: 0.81–1.05); p=0.216	• No difference in 2° outcomes; ARB was safe in this pt population - no angioedema
SUPPORT Sakata et al. 2015 (5) 25637937	Aim: Discover whether addition of ARB to ACE and beta blockers in pts with chronic HF will improve clinical outcomes Study Type: Open label blinded endpoint Size: 1,147	Inclusion Criteria: Pts 20–79 y of age with hypertension, NYHA class II-IV, stable on ACE ± beta blockers Exclusion Criteria: Creatinine >3.0, MI or, revascularization within 6 mo	Intervention: Randomization to olmesartan (578) titrated up to 40 mg as tolerated (578) (mean dose achieved at 5 y, 17.9 mg/d) Comparator: Titration to control BP without use of an ARB (568)	1° endpoint: • Composite of all-cause death, MI, stroke, or HF hospitalization at 4.4 y Results: No significant difference RR: 1.18 (95% CI: 0.96–1.46); p=0.11	• Pts on triple therapy with ACE/ARB/Beta blocker had more of 1° composite outcome, 38.1 vs. 28.2%, HR: 1.47 (95% CI: 1.11–1.95; p=0.006); all-cause death, 19.4 vs. 13.5%, HR: 1.50 (95% CI: 1.01–2.23; p=0.046); and renal dysfunction (21.1 vs. 12.5%, HR: 1.85 (95% CI: 1.24–2.76; p=0.003).
Mineralocorticoids Antagonist					

EMPHASIS subgroup analysis Eschalier et al. 2013 (6) 23810881	Aim: Investigate the safety and efficacy of eplerenone in pts at high risk for hyperkalemia Study Type: Prespecified subgroup analysis of RCT Size: 2,737	Inclusion Criteria: Pts enrolled in EMPHASIS at high risk for hyperkalemia of worsening renal function (>75 y, DM, eGFR <60, or SBP <123) Exclusion Criteria: eGFR<30	Intervention: Randomization to eplerenone Comparator: Placebo	1° endpoint: • Efficacy: Hospitalization for HF or worsening renal failure. Safety: K >5.5, >6.0, <3.5, hospitalization for significant hyperkalemia, hospitalization for worsening renal function Results: Efficacy: reduced composite endpoint. Safety: increased risk of K+ >5.5 mmol/L, hospitalization for hyperkalemia or discontinuation of study medication due to adverse events. No differences from the main trial results in the high-risk subgroups. K >5.5 was increased in the whole cohort and the subgroups, but K >6.0, clinically significant hyperkalemia, and change in eGFR were not substantially higher.	• The beneficial effects of eplerenone were maintained in the high-risk subgroups.
RALES Pitt et al. 1999 (7) 10471456	Aim: To investigate the effect of spironolactone on mortality and morbidity in pts with severe HF. Study Type: RCT Size: 1,663	Inclusion Criteria: NYHA class III, IV; HF≤6 mo, Left EF≤35%, On ACE inhibitors, loop diuretic. Digitalis and vasodilators allowed. Exclusion Criteria: 1° operable VHD (other than mitral or tricuspid), ACHD, unstable angina, 1° heaptic failure, active cancer, life threatening disease, heart transplant, serum Cr ≥2.5 mg/dL, serum K ≥5.0 mmoL/L	Intervention: Spironolactone 25 mg daily (822) Comparator: Placebo (841)	1° endpoint: • Death from all causes Results: • Placebo vs. Spironolactone group (46% vs. 35%; RR: 0.70; 95% CI: 0.60–0.82; p<0.001) • Trial stopped early due to favorable results at 24 mo.	• Reduction in death from cardiac causes and Hospitalization for cardiac causes (p<0.001) • Improvement in NYHA class (p<0.001) • No clinically important safety concerns for electrolytes. Gynecomastia/breast pain more frequent in the spironolactone group (p<0.001)

1° indicates primary; 2°, secondary; ACE, angiotensin-converting enzyme; ARB, angiotensin-receptor blockers; ACHD, adult congenital heart disease; BP, blood pressure; CAD, coronary artery disease; CI, confidence interval; CVD, cardiovasculardisease; CV, cardiovascular; DM, diabetes mellitus, eGFR, estimated glomerular filtration rate; EMPHASIS, Eplerenone in Mild Patients Hospitalization and Survival Study in Heart Failure; HF, heart failure; MI, myocardial infarction; NNH, number needed to harm; NYHA, New York Heart Association; ONTARGET, The Ongoing Telmisartan Alone and in Combination With Ramipril Global Endpoint Trial; pts, patients; PVD, peripheral vascular disease; RCT, randomized controlled trial; RR, relative risk; SBP, systolic blood pressure; SUPPORT, Supplemental Benefit of ARB in Hypertensive Patients With Stable Heart Failure Using Olmesartan; TRANSCEND, the Telmisartan Randomised Assessment Study in ACE Intolerant Subjects With Cardiovascular Disease; and VHD, valvular heart disease.

Search Terms and Date: angiotensin-receptor blockers, ARBs, angiotensin-receptor blocker, ARB, angiotensin-receptor antagonists, angiotensin receptor antagonist, candesartan, irbesartan, losartan, telmisartan, valsartan, olmesartan, AND heart failure or congestive heart failure or CHF or HFrEF AND clinical trial, January 2016.

The ARB evidence table from the 2013 Heart Failure Guideline is included at the end of this document.

The ACE inhibitor evidence table from the 2013 Heart Failure Guideline is also included at the end of this document.

The Beta Blocker evidence table from the 2013 Heart Failure Guideline is included at the end of this document.

Data Supplement 3. RCTs Comparing Pharmacological Treatment for of ARNI With ACE (Section 7.3.2.10)

Study Acronym; Author; Year Published	Aim of Study; Study Type; Study Size (N)	Patient Population	Study Intervention (# patients) / Study Comparator (# patients)	Endpoint Results (Absolute Event Rates, P values; OR or RR; & 95% CI)	Relevant 2° Endpoint; Study Limitations; Adverse Events
IMPRESS Rouleau et al. 2000 (8) 10968433	Aim: Determine if inhibition of neutral endopeptidase and ACE with the vasopeptidase inhibitor omapatrilat is better than ACE inhibition alone with lisinopril Study type: Double blind RCT Size: 573 pts	Inclusion criteria: • Informed consent • Age ≥18 • Stable (>3 mo) symptomatic HF (NYHA class II–IV HF) • Decreased LVEF ≤40 • ≥4 wk dose of ACE inhibitors • Seated SBP ≥90 mm Hg Exclusion criteria: • Uncontrolled hypertension • Acute coronary events within 3 mo • Revascularization within 3 mo • Serum potassium <3.5 or >5.3 mmol/L • Creatinine >221 mcmol/L • Transaminases >2 upper limit of normal • Leucocytes <3.0x10⁹/L, neutrophils <1.5x10⁹/L, or platelets <120x10⁹/L • Use of beta blockers <6 mo • Calcium channel blockers for use other than AF • Pts included in previous RCTs of omapatrilat	Intervention: Omapatrilat (289) target dose 40 mg daily Comparator: Lisinopril (284) target dose 20 mg daily	1° endpoint: Change in exercise duration from baseline to wk 12 Results: Similar exercise duration at 12 wk (p=0.45)	2° endpoint: • No difference in combined endpoint of death and admission for worsening HF (p=0.52) • Combined endpoint of death and comorbidity for worsening HF was better for omapatrilat HR: 0.52 (95% CI: 0.28–0.96; p=0.035) • Angioedema occurred in no pts taking omapatrilat vs. 1 taking enalapril Comments: Vasopeptidase inhibitor omapatrilat did not improve exercise tolerance compared with ACE inhibitor lisinopril
OVERTURE Packer et al. 2002 (9) 12186794	Aim: Determine dual ACE and NEP inhibitors provides greater benefit in pts with HF than ACE inhibitors alone	Inclusion criteria: • NYHA class II–IV HF due to non/ischemic cardiomyopathy for ≥2 mo, or • LVEF ≤30% and hospitalized for HF within 12 mo Exclusion criteria:	Intervention: Omapatrilat (2,886), target dose 40 mg daily achieved 82.5% Comparator: Enalapril (2,884) target dose 10	1° endpoint: Combined risk of death or hospitalization for HF requiring IV treatment Results: No significant difference HR: 0.94 (95%	• Omapatrilat reduced risk of death and hospitalization for chronic HF HR: 0.89 (95% CI: 0.82–0.98; p=0.012). For this analysis, pts were treated with intensification of oral medications.

	Study type: Double blind RCT Size: 5,770 pts	• Surgically correctable or reversible cause of HF • Likely to receive cardiac transplant or left ventricular assist device • Severe 1° pulmonary, renal, or hepatic disease • Hx of intolerance to ACE inhibitors • ACS within 1 mo • Coronary revascularization or an acute cerebral ischemic event within 3 mo • Hx of ventricular tachycardia, ventricular fibrillation, or sudden death who did not have an implantable cardioverter-defibrillation placed and had not fired within 2 mo • Hx or hospitalization or intravenous therapy for HF within 48 h • Intravenous positive inotropic agent within 2 wk • SBP >180 or <90 mm Hg • Heart rate >130 bpm • Serum creatinine >2.5 mg/dL • Serum potassium <3.5 or >5.2 mmol/L	mg BID achieved 86.4%	CI: 0.86–1.03; p=0.187)	• More frequent angioedema with omapatrilat (0.8% vs. 0.5%)
OCTAVE Kostis et al. 2004 (10) 14751650	Aim: Compare safety and efficacy of dual ACE and NEP inhibitors to ACE inhibitors alone Study type: Double blind RCT Size: 25,302 pts	Inclusion criteria: • Age ≥18 • 3 separate BP criteria for 3 groups: Group 1 untreated hypertension (SBP ≥140 mm Hg or DBP ≥90 mm Hg); Group 2 hypertension and persistent mild hypertension (trough SBP 140–159 mm Hg and DBP <100 mm Hg, or trough DBP 90–99 mm Hg and SBP <160 mm Hg); Group 3 hypertension with persistent moderate to severe hypertension (trough SBP 160–179 mm Hg and DBP <110 mm Hg, or trough DBP 100–109 mm Hg and SBP <180 mm Hg) Exclusion criteria: • Contraindication to therapy with ACE inhibitors or angiotensin II receptor antagonists • Hx of angioedema, anaphylaxis, drug-induced or chronic urticarial, or multiple drug sensitivities • Recent hospitalization for MI, unstable angina, stroke, TIA or COPD • Recent treatment for malignancy, chronic renal	Intervention: Omapatrilat target dose 80 mg daily Comparator: Enalapril target dose 40 mg daily	1° endpoints: • Reduction in SBP at wk 8 • Need for new adjunctive antihypertensive therapy by wk 24	2° endpoints: • Reduction in DBP at wk 8 • Reduction in SBP and DBP at wk 24 • BP control (SBP <140 mm Hg and DBP <90 mm Hg) at wk 8 and 24 Comments: • Greater reductions in BP in omapatrilat within each study (p<0.001) • Overall mean reduction in SBP ≥3.6 mm Hg • Larger reductions in BP in black pts with omapatrilat than with enalapril. But overall reduction smaller with both drugs than in other subgroups. • Adverse events, serious adverse events, and deaths were the same for omapatrilat and enalapril

		disease 2° to autoimmune disease, or end-stage renal disease of any etiology • Hypertensive pts treated with ACE inhibitors whose BP placed them in study group 3			• More angioedema with omapatrilat (2.17% vs. 0.68%) • More angioedema in blacks with omapatrilat (5.54% vs. 1.62%) and current smokers (3.93% vs. 0.81%)

1° indicates primary; 2°, secondary; ACE, angiotensin converting enzyme; ACS, acute coronary syndrome; BP, blood pressure; CI, confidence interval; COPD, chronic obstructive pulmonary disease; DPB, diastolic blood pressure; HF, heart failure; Hx, history; IV, intravenous; IMPRESS, Comparison of Vasopeptidase Inhibitor, Omapatrilat, and Lisinopril on Exercise Tolerance and Morbidity; LVEF, left ventricular ejection fraction; MI, myocardial infarction; NYHA, New York Heart Association; NEP, neutral endopeptidase; OVERTURE, Omapatrilat Versus Enalapril Randomized Trial of Utility in Reducing Events; OCTAVE, The Omapatrilat Cardiovascular Treatment vs. Enalapril; pts, patients, RCT, randomized controlled trial; RR, relative risk; SBP, systolic blood pressure; TIA, transient ischemic attack.

Search Terms and Date: March 2016, angioedema, neprilysin inhibitors, omapatrilat.

Data Supplement 4. RCTs Comparing Pharmacological Treatment for Stage C HF*r*EF (Section 7.3.2.11)

Study Acronym; Author; Year Published	Aim of Study; Study Type; Study Size (N)	Patient Population	Study Intervention (# patients) / Study Comparator (# patients)	Endpoint Results (Absolute Event Rates, P values; OR or RR; & 95% CI)	Relevant 2° Endpoint (if any); Study Limitations; Adverse Events
SHIFT HF Böhm et al. 2015 (11) 26508709	Aim: To assess influence of comorbidities on outcomes and ivabradine treatment effect of heart rate reduction in stable HF. Study type: Post hoc analysis of RCT Size: 6,505	Inclusion criteria: Pts ≥18 y of age in sinus rhythm, heart rate at rest ≥70 bpm, MTD for HF meds Exclusion criteria: N/A	Intervention: Ivabradine Comparator: Placebo	1° endpoint: • CV death or HF hospitalization rate increased with the comorbidity load ($p<0.0001$) with most events in pts with >3 comorbidities for both drug and placebo. • Hospitalization rate lower for comorbidity loads of ivabradine	• Number of comorbidities was related to outcomes • Heart rate reduction with Ivabradine is conserved at all comorbidity loads
SHIFT Swedberg K et al. 2010 (12) 20801500 Ivabradine and outcomes in chronic HF (SHIFT)	Aim: To assess the effect of heart rate reduction by the selective sinus-node inhibitor ivabradine on outcomes in HF Study type: randomized,	Inclusion criteria: Over 18 y of age, in sinus rhythm, resting heart rate of ≥70 bpm, stable symptomatic chronic HF (NYHA class II-IV) for ≥4 wk, previous admission to the hospital for HF within 12 mo, LVEF ≤35%	Intervention: Ivabradine Comparator: Placebo	1° endpoint: • Composite of CV death or hospital admission for worsening HF • Primary endpoint: ivabradine better. Event rate 24% vs. 29%. HR 0.82 (0.75–0.90); $p<0.0001$	• Composite of CV death or hospital admission for worsening HF among those receiving at least 50% of target beta blocker dose at time of randomization. All cause death; any CV death; HF hospitalization; all-cause hospitalization; any CV hospitalization; death from HF; composite of CV death HF hospitalization, nonfatal MI. • No difference in all-cause mortality or CV mortality

	double-blind placebo-controlled trial. 677 centers 37 countries Size: 6,558 6,505 analyzed 3,241 ivabradine 3,264 placebo	Exclusion criteria: HF due to congenital heart disease or 1° severe valvular disease. MI within 2 mo, ventricular or AV pacing for ≥40% of the d, AF or flutter, symptomatic hypotension The following treatments not allowed during study: • diltiazem and verapamil (nondihydropyridine CCB) • class I antiarrhythmics • strong inhibitors of CYP450 3A4		• Hospitalization for worsening HF: ivabradine better. 16% vs 21%, HR: 0.74 (95% CI: 0.66–0.83; p<0.001) • Death from HF: ivabradine better. 3% vs. 5%; HF: 0.74 (0.58–0.94); p=0.014	• Ivabradine better for all-cause hospitalization, HF hospitalization, CV hospitalization, and composite 2° endpoint • Analyzed as time to first event. Median follow-up of 22.9 mo • In subgroup analysis, effect limited to those with higher baseline heart rate (≥77 bpm) • Use of devices was low (CRT in 1% and ICD in 4%) • Mean age 61 y • When added to GDEM, including beta blocker at optimal dose, ivabradine reduced adverse events, driven largely by HF mortality or HF hospitalization Adverse Effects: • 1% withdrew due to bradycardia (p<0.001) • Phosphenes 3% (p<0.001) • Comparable across age groups • AF - ivabradine 9% vs. placebo 8% (p=0.012)
SIGNIFY Fox et al. 2014 (13) 25176136	Aim: Assess the mortality-morbidity benefits of Ivabradine in pts with stable CAD without clinical HF Study type: RCT Size: 19,102	Inclusion criteria: Stable CAD without clinical HF and heart rate of ≥70 bpm and in sinus rhythm, persistence and confirmation of ≥1 CV risk factors Exclusion criteria: Serum creatinine >200 mcmol /L, significant anemia, ALT or AST >3 times upper normal value, unstable CV condition, LVEF ≤40%; MI, coronary revascularization, stroke ≤3 mo.	Intervention: Ivabradine (n=9,550) Comparator: Placebo (n=9,552)	1° endpoint: • Composite of CV death and nonfatal MI • Results: No significant difference in incidence of 1° endpoint (HR: 1.08; 95% CI: 0.96–1.20; p=0.20), death from CV causes (HR: 1.10; 95% CI: 0.94–1.28; p=0.25), nonfatal MI (HR: 1.04; 95% CI: 0.90–1.21; p=0.60) and rate of death (HR: 1.06; 95% CI: 0.94–1.21; p=0.35) 1° Safety endpoint:	• Adverse Events: Increased bradycardia, AF, phosphenes and cardiac disorders. • Significant interaction between ivabradine and presence of angina in a subgroup analysis (p=0.02).

				• Incidence of bradycardia higher in Ivabradine group (p=0.001)	
BEAUTIFUL Fox et al. 2008 (14) 18757088	Aim: Assess the mortality-morbidity benefits of Ivabradine in pts with CAD and LV systolic dysfunction Study type: Randomized, double-blind, placebo-controlled Size: 10,917 5,479 ivabradine 5438 placebo	Inclusion criteria: • Pts ≥55 y of age with stable CAD defined as: previous MI, previous revascularization (PCI or surgery), or angiographic evidence of ≥1 stenosis of ≤50%) AND LVEF <40% and end diastolic internal dimension of >56 mm. Sinus rhythm with resting heart rate of ≥60 bpm. • Angina and HF symptoms stable for 3 mo • Appropriate conventional CV medication for 1 mo. Exclusion criteria: MI or coronary revascularization within the previous 6 mo; stroke or TIA within 3 mo, PPM or ICD, valvular disease likely to need surgery within 3 y, SSS, sinoatrial block, congenital long QT, complete AV block, severe or uncontrolled hypertension, NYHA class IV HF	Intervention: Ivabradine n=5,479 Comparator: • Placebo in addition to appropriate CV medication n=5,438	1° endpoint: • Composite of CV death, admission for MI and admission for HF • No difference in composite 1° endpoint (22.5% vs. 22.8%; HR: 1.00; 0.91–1.1; p=0.94) • No differences in any prespecified subgroup.	2° endpoints: 1) All-cause mortality 2) Cardiac death (death from MI or HF or related to a cardiac procedure) 3) CV death (death from a vascular procedure, presumed arrhythmic death, stroke death, other vascular death or sudden death of unknown cause) or admission for HF, 4) Composite of admission for fatal and nonfatal MI or UA 5) Coronary revascularization 6) CV death 7) Admission for HF 8) Admission for MI • No differences in 2° endpoints in overall population. • In subgroup with heart rate of ≥70, ivabradine reduced 1) admission for AMI (fatal and nonfatal) (HR 0.64; 0.49–0.84; p=0.001) 2) composite of admission for AMI or UA (HR 0.78; 0.62–0.97; p=0.023) 3) coronary revascularization (HR 0.7; 0.52–0.93; p=0.16) • 28% in Ivabradine group discontinued medication (vs. 16%), largely due to bradycardia (13% vs. 2%) • No difference in significant adverse effects (23% vs. 23%; p=0.70)

1° indicates primary; 2°, secondary; AV, atrioventricular; AF, atrial fibrillation; AST, *aspartate transaminase*; ALT, *alanine aminotransaminase*; AMI; acute myocardial infarction; CAD, coronary artery disease; CI, confidence interval; CRT, cardiac resynchronization therapy; CV, cardiovascular; CCB, calcium channel blocker; BEAUTIFUL, Morbidity-Mortality Evaluation of the *I*f Inhibitor Ivabradine in Patients With Coronary Disease and Left-Ventricular Dysfunction; bpm, beats per minute; GDEM, guideline-directed evaluation and management; HF, heart failure; HR, hazard ratio; ICD, implantable cardioverter-defibrillator; LVEF, left ventricular ejection fraction; MI, myocardial infarction; MTD, maximal tolerated dose; N/A, not available; NYHA, New York Heart Association; pts, patients; PCI, percutaneous coronary intervention; PPM, permanent pacemaker; RCT, randomized controlled trial; SIGNIFY, Study Assessing the Morbidity–Mortality Benefits of the I_f Inhibitor Ivabradine in Patients with Coronary Artery Disease; SHIFT, Systolic Heart Failure Treatment with the I_f Inhibitor Ivabradine Trial; SSS, sick sinus syndrome; TIA, transient ischemic attack; and UA, unstable angina.

Search Terms and Date: studies identified by chairs in December 2015, one study added by Jan 2016.

2013 HF Guideline Data Supplement 18. ACE Inhibitors (Section 7.3.2.2)

Study Name, Author, Year	Aim of Study	Study Type	Background Therapy	Study Size	Etiology	Patient Population		Endpoints		Mortality	Trial Duration (Years)	Absolute Benefit	P Values & 95% CI:
			Pretrial standard treatment	*N (Total)* *n (Experimental)* *n (Control)*	*Ischemic/ NonIschemic*	*Inclusion Criteria*	*Exclusion Criteria*	*Primary Endpoint*	*Secondary Endpoint*	*1st Year Mortality*			
CONSENSUS 1987 2883575 (15)	To Evaluate influence of enalapril on prognosis of NYHA class IV HF	RCT	Diuretics (spironolactone 53%, mean dose 80mg), digitalis (93%), other vasodilators, except ACEI (ie, nitrates 46%)	253; 127;126	CAD 73%	Severe HF/symptoms at rest/NYHA class IV; Increased heart size >600 mL; BP: 120/75; HR: 80; AF 50%	APE; hemodynamically import aortic/MV stenosis; MI w/in prior 2 mo Unstable angina; planned cardiac surgery; right HF b/c of pulm disease; Cr >300 mmol/L	Mortality	Change in NYHA-FC, LV size, Cr level	52% placebo group and 36% enalapril group (6 mo mortality: 26% in enalpril group and 44% in placebo group)	0.51 y	N/A	Crude mortality at end of 6 mo (primary endpoint), 26% in enalapril group and 44% in placebo group—40% reduction (p =0.002). Mortality was reduced by 31% at 1 y (p=0.001)
10 y FU of CONSENSUS 1999 10099910 (16)	Report on the survival at the 10-y follow up of the pts randomized in CONSENSUS. (1st study to show prognostic improvement by an ACEI. Pts in NYHA class IV HF treated with enalapril or placebo. After study completion all pts were offered open-label enalapril therapy).	10-y open-label follow-up study (via completion of a questionnaire) on the survival status of pts in CONSENSUS -a RCT.	All pts were offered open-label enalapril therapy	315; 77; 58		253 randomized pts included in analysis of time from randomization to death; Survivors (135) of the double-blind period included in analysis of the time from end of double-blind period to death; Severe, NYHA IV		Mortality			10 y		5 pts, all in the enalapril group, were long-term survivors (p=0.004). Averaged over the trial (double-blind plus open-label extension) risk reduction was 30% (p=0.008), 95% CI: 11% - 46%. At end of double-blind study period, mortality considerably higher among pts not receiving open ACEI therapy
SOLVD 1991 2057034 (17)	Study the effect of enalapril on mortality and hospitalization in pts with chronic HF and EF ≤35%	RCT	Diuretics + Digoxin	2569; 1285; 1284	Ischemic heart disease 72%	LVEF <35%; Mild to severe (11% class I/<2% class IV); LVEF 25%; BP: 125/77; HR: 80; AF: 8-12%	Age >80 y; Unstable angina; MI w/in past mo; Cr>2.0 mg/dL	Mortality	Hospitalizations; Incidence of MI; Mortality by specific causes; Combined mortality and morbidity from both SOLVD+/SOLVD-	15.70%	3.45 y	Treating 1000 SOLVD+ pts with enalapril for ~3 y would save ~50 premature deaths and 350 hospitalizations.	Reduced mortality by 16%; (95% CI, 5-26%; p=0.0036)

SOLVD 1992 1463530 (18)	Study effect of ACEIs on total mortality and mortality from CV causes, the development of HF, and hospitalization for HF in pts with EF ≤35%	RCT	No drug treatment for HF	4228; 2111; 2117	History of ischemic heart disease 85%	EF <35%; Asymptomatic; NYHA class I (67%) + II; EF: 28%; BP: 126/78; HR: 75; AF: 4%	As per SOLVD+	Mortality; Combined mortality and the incidence of HF and rate of hospitalization for HF	Incidence of HF and rate of hospitalization for HF		3.12 y		Reduced mortality: p=0.30; 95% CI: -8-21%
SOLVD F/U 2003 12788569 (19)	12-y FU of SOLVD to establish if the mortality reduction with enalapril among pts with HF was sustained, and whether a subsequent reduction in mortality would emerge among those with asymptomatic ventricular dysfunction.	12 y f/u of RCTs [SOLVD+ and SOLVD-]	N/A	6784; 3391; 3393	N/A	Participation in SOLVD+ and SOLVD- Asymptomatic to severe; NYHA I-IV	N/A	Mortality	N/A	N/A	N/A	Enalapril extended median survival by 9.4 mo in the combined trials (95% CI: 2.8–16.5, p=0.004).	In the prevention trial, 50.9% of the enalapril group had died c/w 56.4% of the placebo group (p=0.001). In the treatment trial, 79.8% of the enalapril group had died c/w 80.8% of the placebo group (p=0.01). Combined prevention and treatment trials: HR for death was 0.90 for the enalapril group c/w placebo group (95% CI: 0.84–0.95, p=0.0003).
ATLAS 1999 10587334 (20)	To compare the efficacy and safety of low and high doses of ACEI on the risk of death and hospitalization in chronic HF. than the large doses that have been shown to reduce morbidity and mortality in pts with HF. AIM: Investigate if low doses and high doses of ACEIs have similar benefits.	RCT	N/A	3164; 1596 to the low-dose strategy and 1568 to the high-dose strategy.	CAD 65%	LVEF <=30%; NYHA class II, III, or IV, despite treatment with diuretics for ≥2 mo (Treatment for HF in ED or hospital within 6 mo required for pts in class II); Prior use of digitalis, ACEIs, or vasodilators allowed but not mandated; NYHA II-IV (mainly class II); LVEF 23%; SBP 126 mmHg; HR 80; NYHA class: III (few II and IV)	Acute coronary ischemic event or revascularization procedure within 2 mo; History of sustained or symptomatic ventricular tachycardia; Intolerant of ACEIs; SCr >2.5 mg/dL	Mortality from all causes	Combined risk of all-cause mortality and hospitalization for any reason; CV mortality, CV hospitalizations; All-cause mortality combined with CV hospitalizations; CV mortality combined with CV hospitalizations; Combined risk of fatal and nonfatal MI plus hospitalization for unstable angina		5 y		High-dose group had 8% lower risk of all-cause mortality (p=0.128) and 10% lower risk of CV mortality (p=0.073) than low-dose group. Death or hospitalization for any reason, high-dose group had 12% lower risk than low-dose group, p=0.002. Total number of hospitalizations: high-dose group 13% fewer hospitalizations for any reason (p=0.021), 16% fewer hospitalizations for CV reason (p=0.05), and 24% fewer hospitalizations for HF (p=0.002).
Post-MI ACEI Use													
SAVE, 1992 1386652 (21)	To test the hypothesis that the long-term administration of captopril to survivors	RCT	Beta-blockers 36%; Digitalis 26%; Nitrates 51%	2231; 1115; 1116	Ischemic 100%	Alive 3 d after MI; LVEF <40%; >21 y of age, but	Failure to undergo randomization within 16 d after the MI; Relative contraindication to	Mortality from all causes	Mortality from CV causes; Mortality combined with a decrease in the EF of at least 9 units in		3.5 y		Mortality from all causes was significantly reduced in the captopril group (228 deaths, or 20%) as c/w the placebo group (275 deaths, or 25%); the RR: 19%

	of acute MI who had baseline LV dysfunction but did not have overt HF requiring vasodilator therapy would reduce mortality, lessen deterioration in cardiac performance, and improve clinical outcome.					<80; Killip class I — 60% (60% of the ps did not have even transient pulmonary congestion at baseline/the time of their acute MI; EF 31%; BP 113/70; HR 78;	the use of an ACEIs or the need for such an agent; SCr > 2.5 mg/dl		surviving pts; CV morbidity (development of severe CHF or the recurrence of MI); Combination of CV mortality and morbidity; 2 endpoints of severe HF (treatment failure): 1st, development of overt HF necessitating treatment with ACEI and 2nd, hospitalization to treat CHD.				(95% CI, 3-32%; p=0.019). RR:21% (95% CI, 5 -35%; p=0.014) for death from CV causes, 37% (95% CI, 20-50%; p<0.001) for the development of severe HF, 22% (95% CI, 4-37%; p=0.019) for CHF requiring hospitalization, and 25% (95% CI, 5-40%; p=0.015) for recurrent MI.
AIRE 1993 8104270 (22)	Investigated the effect of therapy with ACEI ramipril, on survival in pts who had shown clinical evidence of HF at any time after an acute MI. Also, to compare the incidences of progression to severe or resistant HF, nonfatal reinfarction and stroke between the 2 groups.	RCT		2006; 1014; 992		Aged ≥18 y, with a definite acute MI 3-10 d before randomization; Clinical evidence of HF at any time since acute MI	Use of an ACEI considered to be mandatory	Mortality from all causes			1.3 y		Mortality from all causes was significantly lower for pts on ramipril compared to pts on placebo. RR: 27%; 95% CI: 11-40%; p=0.002. Prespecified secondary outcomes: risk reduction of 19% for the 1st validated outcome—namely, death, severe/resistant HF, MI, or stroke (95% CI: 5% - 31%; p=0.008).
TRACE 1995 7477219 (23)	To determine whether pts who LV dysfunction soon after MI benefit from long-term oral ACE inhibition.	RCT	Beta blocker 16%; Calcium antagonist 28%; Diuretic 66%; Nitrates 53%; Digoxin 28%.	1749; 876; 873	Ischemic 100%	Consecutive pts >18 y hospitalized with MI; Criteria for MI: chest pain or electrocardiographic changes, accompanied by >2X increase in ≥1 cardiac enzymes; LV dysfunction (EF <35%); NYHA class 1 - 41%; BP 121/76; HR 81	Contraindication to ACEI or a definite need for them; Severe, uncontrolled DM; Hyponatremia (<125 mmol/L); Elevated SCr level (2.3 mg/dL)	Death from any cause	Death from a CV cause, sudden death; Progression to severe HF (hospital admission for HF, death due to progressive HF, or HF necessitating open-label ACEI); Recurrent infarction (fatal or nonfatal); Change in the wall-motion index (EF)	The mortality from all causes at 1 y was 24%.		24 lives were saved after 1 mo of treating 1,000 pts	During the study period, 304 pts in the trandolapril group died (34.7%), as did 369 in the placebo group (42.3%). RR: 0.78 (95% CI, 0.67 - 0.91; p=0.001). In every subgroup, treatment with trandolapril was associated with a reduction in risk.

ACEI indicates angiotensin-converting-enzyme inhibitor; AF, atrial fibrillation; AIRE, Acute Infarction Ramipril Efficacy; APE, acute pulmonary embolism; ATLAS, Assessment of Treatment with Lisinopril and Survival; BP, blood pressure; CAD, coronary artery disease; CHD, chronic heart disease; CHF, congestive heart failure; CONSENSUS Cooperative North Scandinavian Enalapril Survival Study; Cr, creatinine; CV, cardiovascular; C/W, compared with; DM, diabetes mellitus; ED, emergency department; FU, follow-up; HF, heart.

2013 HF Guideline Data Supplement 19. ARBs (Section 7.3.2.3)

Study Name, Author, Year	Aim of Study	Study Type	Background Therapy	Study Size	Etiology	Patient Population		Severity	Endpoints		Mortality	Trial Duration (Y)	Statistical Results
			Pre-trial standard treatment.	*N (Total) n (Experimental) n (Control)*	*Ischemic/ Non-Ischemic*	*Inclusion Criteria*	*Exclusion Criteria*		*Primary Endpoint*	*Secondary Endpoint*	*1st Y Mortality*		
CHARM Alternative; Granger et al; (2003) 13678870 (24)	Discover whether ARB could improve outcome in pts not taking an ACEI (intolerant)	RCT	Diuretics, Beta-blockers (55%), spironolactone 24%, Digoxin 45-46%	2028; 1013; 1015	Ischemic 67-70%	Symptomatic HF, EF <40%, no ACEI (b/c of intolerance)		NYHA II-IV; mild to severe (<4% class IV); EF: 30%; BP: 130/70; HR: 74-75; AF: 25-26%	Composite of CV death or hospital admission for CHF	CV death, hospital admission for CHF or nonfatal MI; CV death, CHF admission, nonfatal MI, nonfatal stroke; CV death, CHF admission, nonfatal MI, nonfatal stroke, coronary revascularization; Death (any cause); New DM		2.8 y	Absolute reduction of 7 major events per 100 pts threated - NNT 14 pts to prevent 1 CV death or hospitalization. HR: 0.77 (95% CI: 0.67-0.89); p=0.0004
CHARM-ADDED; McMurray et al; (2003) 13678869 (25)	To investigate if ARB + ACEI in pts with chronic HF improve clincal outcomes	RCT	Beta blocker-55%; spironolactone 17%; Digoxin 58-59%	2548; 1276; 1272	Ischemic 62-63%	Symptomatic HF; EF <40%; Treatment with ACEI; Age >18 y		NYHA class II-IV; mild to severe (<3% class IV); EF 28%; BP 125/75; HR 74; AF 27%	Composite of CV death or hospital admission for CHF	CV death, hospital admission for CHF or nonfatal MI; CV death, CHF admission, nonfatal MI, nonfatal stroke; CV death, CHF admission, nonfatal MI, nonfatal stroke, coronary revascularization; Death (any cause); New DM		3.4 y	Absolute reduction of 4.4 pts with events per 100 pts treated- NNT of 23 to prevent 1 first event of CV death or CHF hospitalization. RR: 0.85 (95% CI: 0.75-0.96); p=0.011
VALIANT; Pfeffer et al; (2003) 14610160 (26)	Compare the effect of an ARB, ACEI and the combination of the 2on mortality	Randomized double blind multicenter trial	Beta-blockers; ASA	14,703 Valsartan:4909 Captopril-: 4909 VAL + CAP: 4885	Ischemic 100% (MI inclusion criteria)	Age >18 y; Acute MI complicated by HF; LV systolic dysfunct (EF <35%), (<40% on radionuclide ventriculography); SBP >100 mmHg; Cr <2.5 mg/dL	Prior intolerance or contra-indication to ACEI/ ARB	NYHA I-IV; asymptomatic-severe, EF 35%; BP: 123/72; HR: 76	Death from any cause		12.5% VAL 12.3% VAL--CAP 13.2% CAP	2.1 y	VAL and CAP: 1.0 (97.5% CI-- 0.90-1.11); p=0.98 ; VAL+CAP and CAP: 0.98 (97.5% CI-- 0.89-1.09); p=0.73
Val-HeFT; Cohn et al; (2001) 11759645 (27)	Evaluate long term effects of adding ARB to standard therapy for HF	RCT	Diuretics; Digoxin 67%; Beta blocker 35%; ACEI 93%	5010; 2511; 2499	Ischemic 57%	Age >18 y; NYHA II, II, IV; At least 2 wk of background meds including ACEIs; EF <40% and LVID >2.9 cm/BSA		NYHA II-III, IV (only ~2% class IV); Mild to severe; EF 27%; BP 123/76; AF 12%	Mortality; Combined endpoint of mortality and morbidity	Change in EF; • NYHA class, QoL scores; Signs and symptoms of HF		1.92 y	Mortality similar for the 2 treatment groups. For the combined endpoint: RR: 0.87; 97.5% CI, 0.77-0.97; p=0.009
HEAAL study; Lancet 2009; 374: 1840-48. 19922995 (28)	Compared the effects of high-dose vs low-dose losartan on clinical outcomes in pts with HF.	RCT	Diuretic drugs (77%), beta blockers (72%), and ARBs (38%).	3846 losartan 150 mg (n=1927) or 50 mg daily (n=1919).	IHD 64%	>18 y; NYHA class II–IV; LVEF <40%, with stable CV medical therapy for at least 2 wk; Intolerance to ACEI; Investigators encouraged to start beta blocker and titrate to a maximum, whenever possible	Pregnancy or lactation; known intolerance to ARBs; Systolic arterial blood pressure <90 mm Hg; Significant stenotic valvular heart disease; Active myocarditis; active pericarditis; Planned heart transplantation w/in 6 mo; coronary angioplasty, CABG, acute MI, UA pectoris, cerebrovascular accident, or TIA within the previous 12 wk; Suspected significant renal	NYHA II-IV (70% II); EF: 33%; BP: 124/77; HR: 71; AF; 28%	Death or admission for HF	Composite endpoint of death or CV admission. Additional prespecified outcomes included: death, death or all-cause admission, CV death, all-cause admission, CV admission, admission for HF, and changes in the severity of heart disease		4.7 y median f/u	Treating pts with 150 mg dose instead of 50 mg dose would result in 1 additional pt w/out the primary event at 4 y for every 31 pts treated. Composite: 828 (43%) pts in 150 mg group vs. 889 (46%) in 50 mg group died or admitted for HF (HR: 0.90; 95% CI: 0.82-0.99; p=0.027) • Components: 635 pts in 150 mg group vs. 665 in 50 mg group died (HR: 0.94, 95% CI: 0.84-1.04; p=0.24), and 450 vs. 503 pts admitted for HF (0.87, 0.76–0.98; p=0.025)

							artery stenosis							
CHARM-Overall 13678868 (29)	Aimed to find out whether the use of an ARB could reduce mortality and morbidity.	RCT-parallel, randomized, double-blind,	Diuretics 83% Beta blockers 55% ACEI 43% Spironolactone 17% Digoxin 43%	7601 pts (7599 with data) 3803 3796		>18 y; NYHA class II–IV for at least 4 wk; 3 distinct populations: pts with LVEF <40% who were not receiving ACEIs (previous intolerance) or who were currently receiving ACE, and pts with LVEF >40%	SCr > 265 mcmol /L, serum potassium >5.5 mmol/L Bilateral renal artery stenosis; symptomatic hypotension Women of childbearing potential not using adequate contraception; Critical aortic or mitral stenosis; MI, stroke, or open-heart surgery in the previous 4 wk; Use of an ARB in the previous 2 wk	NYHA II-IV NYHA II-IV Only 3% class IV	The primary outcome of the overall program: all-cause mortality; For all the component trials: CV death or hospital admission for CHF.		The annual CV death rate among the placebo group who had reduced LVEF was around 9% and was only 4% in the placebo group of CHARM-Preserved.	3.1 y	886 (23%) pts in candesartan and 945 (25%) in placebo group died (unadjusted HR: 0.91; 95% CI: 0.83–1.00; p=0.055; covariate aHR: 0.90 95% CU: 0.82–0.99; p=0.032) • Fewer CV deaths (691 [18%] vs 769 [20%], unadjusted HR: 0.88; 95% CI: 0.79–0.97; p=0.012; covariate aHR: 0.87; 95% CI: 0.78–0.96; p=0.006) • Hospital admissions for CHF (757 [20%] vs 918 [24%], p<0.0001)

ACEI indicates angiotensin-converting-enzyme inhibitor; AF, atrial fibrillation; ARB, angiotensin receptor blockers; ASA, aspirin; BP, blood pressure; BSA, body surface area; CABG, coronary artery bypass graft; CHARM, Candesartan in Heart Failure: Assessment of Reduction in Mortality and Morbidity; CHD, chronic heart disease; CHF, congestive heart failure; Cr, creatinine; CV, cardiovascular; DM, diabetes mellitus; EF, ejection fraction; FU, follow-up; HEAAL study, effects of high-dose versus low-dose losartan on clinical outcomes in patients with heart failure; HF, heart failure; HR, heart rate; IHD, ischemic heart disease; LV, left ventricular; LVD, left ventricular dilatation; MI, myocardial infarction; MV, mitral valve; N/A, not applicable; NNT, number needed to treat; NYHA, New York Heart Association; QoL, quality of life; pts, patients; SBP, systolic blood pressure; RCT, randomized control trial; SCr, serum creatinine; TIA, transient ischemic attack; UA, unstable angina; Val-HeFT, Valsartan Heart Failure Trial; and VALIANT, Valsartan in Acute Myocardial Infarction.

2013 HF Guideline Data Supplement 20. Beta Blockers (Section 7.3.2.4)

Study Name, Author, Year	Aim of Study	Study Type	Background Therapy	Study Size	Etiology	Patient Population		Severity	Endpoints		Mortality		Trial Duration	Statistical Results
				N (Total) *n (Experimental)* *n (Control)*		*Inclusion Criteria*	*Exclusion Criteria*		*Primary Endpoint*	*Secondary Endpoint*	*Annualized Mortality*	*1st Y Mortality*		
CIBIS II CIBIS II investigators and committee members (1999) 10023943 (30)	Investigate the efficacy of bisoprolol in decreasing all-cause mortality in chronic HF	RCT-multicenter double-blind randiomised placebo controlled trial (Europe)	Diuretics + ACEI; [amiodarone allowed--14-l6%]	2647; 1327; 1320	Documented Ischemic 50%	NYHA class lll or IV EF: <35% 18-80 y old	Uncontrolled HTN; MI/UA w/in previous 3 mo; PTCA/CABG w/in previous 6 mo; AV-block >1st degree w/o PPM; Heart rate < 60bpm; resting SBP <100mmHg; renal failure; Reversible obstruct lung disease; Use of beta blocker	Moderate to severe. Mean BP: 130/80; Mean HR: 80; Mean EF: 28%; Mean LVEDD: 6.7 cm; AF: 20%	All-cause mortality	All-cause hospital admissions All CV deaths Combined endpoints Permanent treatment withdrawal	13.2% Placebo group 8.8% Treatm't group	N/A	1.3 y	HR: 0.66 (95% CI: 0.54-0.81); p<0.0001
MERIT-HF; MERIT study Group; (1999) 10376614 (31)	Investigate whether Metoprolol CR/XL lowered mortality in pts with decreased EF and symptoms of HF	RCT--multicenter double-blind randiomised placebo controlled trial (Europe + USA)	Diuretics + ACEI [Amiodarone NOT allowed]	3991; 1991; 2001	Ischemic 65%	NYHA ll-lV; 40-80 y old; LVEF <40% (36-40 if 6-min walk <450m); heart rate >68 bpm	MI/UA w/in 28 d; Contra-indication or current use of beta blocker; PTCA/CABG w/in 4 mo Planned transplant or ICD; Heart block >1st degree w/o PPM; SBP <100mmHg	Mild to severe. Mean BP: 130/78; Mean HR: 78; Mean EF 28%; AF 16-17%	All-cause mortality All-cause mortality in combination with all-cause admission to hospital	N/A	11.0% Placebo group 7.2% Treatm't group	N/A	1 y	Treatment of 27 pt for 1 y can prevent 1 death. 0.66 (95% CI: 0.53-0.81); p=0.00009

COPERNICUS; Packer et al; (2002) 12390947 (32)	Investigate whether Carvadiolo is beneficial in severe HF	RCT--double blind	Diuretics (PO or IV) + ACEI (or ARB); [Amiodarone allowed 17-18%]	2289; 1156; 1133	Ischemic 67%	Euvolumic NYHA class IV; LVEF <25%; No positive inotropes or vasodilators w/in 4 d	Pt requiring hospitalized intensive care; Use of positive inotropes or IV; vasodilators w/in 4-d; Coronary revascularization/MI/CVA/ sign VT or VF w/in 2 mo; SBP < 85 mmHg, Heart rate <68, Cr >2.8 mg/dL	Severe Mean BP: 123/76; Mean HR: 83; Mean EF 20%;	All-cause mortality	Combined risk of death or hospitalization-any reason; Combined risk of death or hospitalization--CV reason; Combined risk of death or hospitalization--HF reason; Pt global assessment	19.7% placebo [24.0% in pts with recent or recurrent cardiac decompensations]	18.5% in placebo group 11.4% in Carvedilol group	10.4 mo	Treating 1000 pt for 1 y led to savings of 70 premature deaths p=0.0014
SENIORS; Flather et al; (2005) 15642700 (33)	Assess effects of the beta blocker Nebivolol in pts >70 y regardless of EF.	RCT	Diuretics + ACEI (+aldosterone antagonist in 29%)	2128; 1067; 1061	Prior h/o CAD in 69%	Age >70 CHF with 1 of the following: hospitalization with CHF w/in a year or EF <35% w/in the past 6 mo	New HF therapy w/in 6 wk or change in drug therapy w/in 2 wk Contraindication to beta blockers, current use of beta blockers Significant renal dysfunction CVA w/in 3 mo.	Mild to severe Mean BP: 139/81; Mean HR: 79; Mean EF 36% (1/3 with EF >35%);	Composite of all-cause mortality or CV hospital admission	All-cause mortality Composite of all-cause mortality or all-cause hospital admissions All cause hospital admissions CV hospital admissions CV mortality Composite of CV mortality or CV hospital admissions NYHA class assessment; 6 MWT	N/A	N/A	1.75 y	Absolute risk reduction 4.2%; 24 pts would need to be treated for 21 mo to avoid one event RR: 0.86; 95% CI: 0.74-0.99; p=0.039
A Trial of the Beta-Blocker Bucindolol in Pt with Advanced Chronic HF The Beta-Blocker Evaluation of Survival Trial Investigators 11386264 (34)	Designed to determine whether bucindolol hydrochloride, a nonselective beta-adrenergic blocker and mild vasodilator, would reduce the rate of death from any cause among pt with advanced HF and to assess its effect in various subgroups defined by ethnic background and demographic criteria — specifically women and members of minority groups.	RCT	ACEIs (if tolerated) [91% ACE; 7% ARB], for at least 1 mo. Before the publication of the results of the DIG trial, 12 digoxin therapies were required, but thereafter its use became discretionary [DIG 94%].	2708; 1354; 1354	Ischemic 59%	NYHA class III or IV HF LVEF <35% >18 y	Reversible cause of HF present Candidates for heart transplantation Cardiac revascularization procedure within the previous 60 d UA Heart rate <50 bpm, SBP <80mmHg Decompensated HF.	NYHA III or IV (92% class III) EF 23%; HR 82; BP 117/71; AF 12%	Death from any cause	Death from CV causes (death due to pump failure or an ischemic event or sudden death) Hospitalization for any reason Hospitalization because of HF Composite of death or heart transplantation LVEF at 3 and 12 mo MI; QoL; and any change in the need for concomitant therapy	For pt in NYHA functional class III, the annual mortality rate was 16% in the placebo group; For pt with NYHA class IV, the annual mortality rate in the placebo group was 28% **Overall**: annual mortality of 17% in placebo group c/w 15% in the bucindolol group.	N/A	~2 y	449 pt in placebo group (33%) died, 411 in the bucindolol group (30%; HR: 0.90; 95% CI, 0.78-1.02; unadjusted p=0.10; adjusted p=0.13)
COMET; Poole-Wilson et al; (2003) 12853193 (35)	To compare the effects of carvedilol and metoprolol on clinical outcome in pts with HF	RCT	Diuretics, ACEIs	3029; 1511 carvedilol; 1518 metoprolol tartrate	N/A	NYHA class II-IV EF <35% Previous CV admission	N/A	Mild to severe	All-cause mortality Composite endpoint of all-cause mortality, or all-cause admission	N/A	N/A	N/A	4.8 y	All-cause mortality 34% carvedilol and 40% metoprolol (HR: 0.83; 95% CI 0.74-0.93; p=0.0017)

(CIBIS) III; 2005 16143696 (36)	Sufficient data do not currently exist to establish the optimum order of initiating chronic HF therapy (ACEI vs. beta blocker). This was the objective of the CIBIS III trial-- it compared the effect on mortality and hospitalization of initial monotherapy with either bisoprolol or enalapril for 6 mo, followed by their combination for 6 to 24 mo.	Multicenter, prospective, randomized, open-label, blinded endpoint evaluation (PROBE) trial,24 with 2 parallel groups.	Diuretics 84%; Digoxin 32%	1010 Bisoprolol 505; Enalapril 505	CAD 62%	>65 y, NYHA class II or III, and LVEF <35% (By echo within the 3 mo) Clinically stable HF (without clinically relevant fluid retention or diuretic adjustment within 7 d)	Treatment with an ACEI, an ARB, or a beta blocker for >7 d during the 3 mo before randomization Heart rate at rest <60 bpm without a functioning pacemaker Supine SBP <100 mm Hg at rest SCr≥220 mmol/L AV block>1° without a functioning pacemaker Obstructive lung disease contraindicating bisoprolol treatment	NYHA II or III; mild to moderate CHF LVEF 29%; Heart rate 79; SBP 134	The primary endpoint was time-to-the-first-event of combined all-cause mortality or all-cause hospitalization	Combined endpoint at the end of the monotherapy phase and the individual components of the primary endpoint, at study end and at the end of the monotherapy phase. CV death CV hospitalization	N/A	N/A	Mean of 1.22±0.42 y (maximum of 2.10 y).	In the ITT sample, 178 pt (35.2%) with a primary endpoint in the bisoprolol-1st group, and 186 (36.8%) in the enalapril-1st group (absolute difference -1.6%; 95% CI: -7.6 to 4.4%; HR: 0.94; 95% CI: 0.77–1.16; noninferiority for bisoprolol-first versus enalapril-1st treatment, p=0.019)

ACEI indicates angiotensin-converting-enzyme inhibitor; AF, atrial fibrillation; ARB, angiotensin receptor blocker; AV, atrioventricular; BP, blood pressure; CABG, coronary artery bypass graft; CHF, congestive heart failure; CIBIS II, Cardiac Insufficiency Bisoprolol Study II; COMET, Carvedilol Or Metoprolol European Trial; COPERNICUS, carvedilol prospective randomized cumulative survival; Cr, creatinine; CR/XL, controlled release/extended release; CV, cardiovascular; CVA, cerebrovascular accident; c/w, compared with; DIG, Digitalis Investigation Group; EF, ejection fraction; HF, heart failure; h/o, history of; HR, hazard ratio; ICD, ICD, implantable cardioverter defibrillator; ITT, intent to treat; MERIT-HF, Metoprolol CR/XL Randomised Intervention Trial in Congestive Heart Failure; MI, myocardial infarction; MWT, minute walk test; NYHA, New York Heart Association; PPM, permanent pacemaker; PTCA, percutaneous transluminal coronary angioplasty; Pts, patients; QoL, quality of life; RCT, randomized control trial; RR, relative risk; SBP, systolic blood pressure; SCr, serum creatinine; UA, unstable angina; USA, United States of America; VF, ventricular fibrillation; VT, ventricular tachycardia; and w/o, without.

References

1. Solomon SD, Zile M, Pieske B, et al. The angiotensin receptor neprilysin inhibitor LCZ696 in heart failure with preserved ejection fraction: a phase 2 double-blind randomised controlled trial. Lancet. 2012;380:1387-95.
2. McMurray JJ, Packer M, Desai AS, et al. Angiotensin-neprilysin inhibition versus enalapril in heart failure. N Engl J Med. 2014;371:993-1004.
3. Yusuf S, Teo KK, Pogue J, et al. Telmisartan, ramipril, or both in patients at high risk for vascular events. N Engl J Med. 2008;358:1547-59.
4. Yusuf S, Teo K, Anderson C, et al. Effects of the angiotensin-receptor blocker telmisartan on cardiovascular events in high-risk patients intolerant to angiotensin-converting enzyme inhibitors: a randomised controlled trial. Lancet. 2008;372:1174-83.
5. Sakata Y, Shiba N, Takahashi J, et al. Clinical impacts of additive use of olmesartan in hypertensive patients with chronic heart failure: the supplemental benefit of an angiotensin receptor blocker in hypertensive patients with stable heart failure using olmesartan (SUPPORT) trial. Eur Heart J. 2015;36:915-23.
6. Eschalier R, McMurray JJ, Swedberg K, et al. Safety and efficacy of eplerenone in patients at high risk for hyperkalemia and/or worsening renal function: analyses of the EMPHASIS-HF study subgroups (Eplerenone in Mild Patients Hospitalization And SurvIval Study in Heart Failure). J Am Coll Cardiol. 2013;62:1585-93.
7. Pitt B, Zannad F, Remme WJ, et al. The effect of spironolactone on morbidity and mortality in patients with severe heart failure. Randomized Aldactone Evaluation Study Investigators. N Engl J Med. 1999;341:709-17.
8. Rouleau JL, Pfeffer MA, Stewart DJ, et al. Comparison of vasopeptidase inhibitor, omapatrilat, and lisinopril on exercise tolerance and morbidity in patients with heart failure: IMPRESS randomised trial. Lancet. 2000;356:615-20.
9. Packer M, Califf RM, Konstam MA, et al. Comparison of omapatrilat and enalapril in patients with chronic heart failure: the Omapatrilat Versus Enalapril Randomized Trial of Utility in Reducing Events (OVERTURE). Circulation. 2002;106:920-6.
10. Kostis JB, Packer M, Black HR, et al. Omapatrilat and enalapril in patients with hypertension: the Omapatrilat Cardiovascular Treatment vs. Enalapril (OCTAVE) trial. Am J Hypertens. 2004;17:103-11.
11. Bohm M, Robertson M, Ford I, et al. Influence of Cardiovascular and Noncardiovascular Co-morbidities on Outcomes and Treatment Effect of Heart Rate Reduction With Ivabradine in Stable Heart Failure (from the SHIFT Trial). Am J Cardiol. 2015;116:1890-7.
12. Swedberg K, Komajda M, Bohm M, et al. Ivabradine and outcomes in chronic heart failure (SHIFT): a randomised placebo-controlled study. Lancet. 2010;376:875-85.
13. Fox K, Ford I, Steg PG, et al. Ivabradine in stable coronary artery disease without clinical heart failure. N Engl J Med. 2014;371:1091-9.
14. Fox K, Ford I, Steg PG, et al. Ivabradine for patients with stable coronary artery disease and left-ventricular systolic dysfunction (BEAUTIFUL): a randomised, double-blind, placebo-controlled trial. Lancet. 2008;372:807-16.
15. Effects of enalapril on mortality in severe congestive heart failure. Results of the Cooperative North Scandinavian Enalapril Survival Study (CONSENSUS). The CONSENSUS Trial Study Group. N Engl J Med. 1987;316:1429-35.
16. Swedberg K, Kjekshus J, Snapinn S. Long-term survival in severe heart failure in patients treated with enalapril. Ten year follow-up of CONSENSUS I. Eur Heart J. 1999;20:136-9.
17. Effect of enalapril on survival in patients with reduced left ventricular ejection fractions and congestive heart failure. The SOLVD Investigators. N Engl J Med. 1991;325:293-302.
18. Effect of enalapril on mortality and the development of heart failure in asymptomatic patients with reduced left ventricular ejection fractions. The SOLVD Investigattors. N Engl J Med. 1992;327:685-91.
19. Jong P, Yusuf S, Rousseau MF, et al. Effect of enalapril on 12-year survival and life expectancy in patients with left ventricular systolic dysfunction: a follow-up study. Lancet. 2003;361:1843-8.
20. Packer M, Poole-Wilson PA, Armstrong PW, et al. Comparative effects of low and high doses of the angiotensin-converting enzyme inhibitor, lisinopril, on morbidity and mortality in chronic heart failure. ATLAS Study Group. Circulation. 1999;100:2312-8.
21. Pfeffer MA, Braunwald E, Moye LA, et al. Effect of captopril on mortality and morbidity in patients with left ventricular dysfunction after myocardial infarction. Results of the survival and ventricular enlargement trial. The SAVE Investigators. N Engl J Med. 1992;327:669-77.

22. Effect of ramipril on mortality and morbidity of survivors of acute myocardial infarction with clinical evidence of heart failure. The Acute Infarction Ramipril Efficacy (AIRE) Study Investigators. Lancet. 1993;342:821-8.
23. Kober L, Torp-Pedersen C, Carlsen JE, et al. A clinical trial of the angiotensin-converting-enzyme inhibitor trandolapril in patients with left ventricular dysfunction after myocardial infarction. Trandolapril Cardiac Evaluation (TRACE) Study Group. N Engl J Med. 1995;333:1670-6.
24. Granger CB, McMurray JJ, Yusuf S, et al. Effects of candesartan in patients with chronic heart failure and reduced left-ventricular systolic function intolerant to angiotensin-converting-enzyme inhibitors: the CHARM-Alternative trial. Lancet. 2003;362:772-6.
25. McMurray JJ, Ostergren J, Swedberg K, et al. Effects of candesartan in patients with chronic heart failure and reduced left-ventricular systolic function taking angiotensin-converting-enzyme inhibitors: the CHARM-Added trial. Lancet. 2003;362:767-71.
26. Pfeffer MA, McMurray JJ, Velazquez EJ, et al. Valsartan, captopril, or both in myocardial infarction complicated by heart failure, left ventricular dysfunction, or both. N Engl J Med. 2003;349:1893-906.
27. Cohn JN, Tognoni G. A randomized trial of the angiotensin-receptor blocker valsartan in chronic heart failure. N Engl J Med. 2001;345:1667-75.
28. Konstam MA, Neaton JD, Dickstein K, et al. Effects of high-dose versus low-dose losartan on clinical outcomes in patients with heart failure (HEAAL study): a randomised, double-blind trial. Lancet. 2009;374:1840-8.
29. Pfeffer MA, Swedberg K, Granger CB, et al. Effects of candesartan on mortality and morbidity in patients with chronic heart failure: the CHARM-Overall programme. Lancet. 2003;362:759-66.
30. CBIS II Authors. The Cardiac Insufficiency Bisoprolol Study II (CIBIS-II): a randomised trial. Lancet. 1999;353:9-13.
31. Effect of metoprolol CR/XL in chronic heart failure: Metoprolol CR/XL Randomised Intervention Trial in Congestive Heart Failure (MERIT-HF). Lancet. 1999;353:2001-7.
32. Packer M, Coats AJ, Fowler MB, et al. Effect of carvedilol on survival in severe chronic heart failure. N Engl J Med. 2001;344:1651-8.
33. Flather MD, Shibata MC, Coats AJ, et al. Randomized trial to determine the effect of nebivolol on mortality and cardiovascular hospital admission in elderly patients with heart failure (SENIORS). Eur Heart J. 2005;26:215-25.
34. A trial of the beta-blocker bucindolol in patients with advanced chronic heart failure. N Engl J Med. 2001;344:1659-67.
35. Poole-Wilson PA, Swedberg K, Cleland JG, et al. Comparison of carvedilol and metoprolol on clinical outcomes in patients with chronic heart failure in the Carvedilol Or Metoprolol European Trial (COMET): randomised controlled trial. Lancet. 2003;362:7-13.
36. Willenheimer R, van Veldhuisen DJ, Silke B, et al. Effect on survival and hospitalization of initiating treatment for chronic heart failure with bisoprolol followed by enalapril, as compared with the opposite sequence: results of the randomized Cardiac Insufficiency Bisoprolol Study (CIBIS) III. Circulation. 2005;112:2426-35.