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
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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)

<table>
<thead>
<tr>
<th>CLASS (STRENGTH) OF RECOMMENDATION</th>
<th>LEVEL (QUALITY) OF EVIDENCE‡</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>CLASS I (STRONG)</strong></td>
<td><strong>LEVEL A</strong></td>
</tr>
<tr>
<td>Benefit &gt;&gt;&gt; Risk</td>
<td>High-quality evidence† from more than 1 RCT</td>
</tr>
<tr>
<td></td>
<td>Meta-analyses of high quality RCTs</td>
</tr>
<tr>
<td></td>
<td>One or more RCTs corroborated by high-quality registry studies</td>
</tr>
<tr>
<td><strong>CLASS IIa (MODERATE)</strong></td>
<td><strong>LEVEL B-R</strong></td>
</tr>
<tr>
<td>Benefit &gt;&gt; Risk</td>
<td>(Randomized)</td>
</tr>
<tr>
<td></td>
<td>Moderate-quality evidence† from 1 or more RCTs</td>
</tr>
<tr>
<td></td>
<td>Meta-analyses of moderate-quality RCTs</td>
</tr>
<tr>
<td><strong>CLASS IIb (WEAK)</strong></td>
<td><strong>LEVEL B-NR</strong></td>
</tr>
<tr>
<td>Benefit ≈ Risk</td>
<td>(Nonrandomized)</td>
</tr>
<tr>
<td></td>
<td>Moderate-quality evidence† from 1 or more well-designed, well-executed nonrandomized studies, observational studies, or registry studies</td>
</tr>
<tr>
<td></td>
<td>Meta-analyses of such studies</td>
</tr>
<tr>
<td><strong>CLASS III: No Benefit (MODERATE)</strong></td>
<td><strong>LEVEL C-LD</strong></td>
</tr>
<tr>
<td>Benefit = Risk</td>
<td>(Limited Data)</td>
</tr>
<tr>
<td>(Generally, LOE A or B use only)</td>
<td>Randomized or nonrandomized observational or registry studies with limitations of design or execution</td>
</tr>
<tr>
<td></td>
<td>Meta-analyses of such studies</td>
</tr>
<tr>
<td><strong>CLASS III: Harm (STRONG)</strong></td>
<td><strong>LEVEL C-EO</strong></td>
</tr>
<tr>
<td>Risk &gt; Benefit</td>
<td>(Expert Opinion)</td>
</tr>
<tr>
<td></td>
<td>Consensus of expert opinion based on clinical experience</td>
</tr>
</tbody>
</table>

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>
<thead>
<tr>
<th>COR</th>
<th>LOE</th>
<th>Recommendations</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>ACE: A</td>
<td>The clinical strategy of inhibition of the renin-angiotensin system with ACE inhibitors (Level of Evidence: A) (9-14), OR ARBs (Level of Evidence: A) (15-18), OR ARNI (Level of Evidence: B-R) (19) in conjunction with evidence-based beta blockers (20-22), and aldosterone antagonists in selected patients (23, 24), is recommended for patients with chronic HFrEF to reduce morbidity and mortality.</td>
</tr>
<tr>
<td></td>
<td>ARB: A</td>
<td>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>
<tr>
<td></td>
<td>ARNI: B-R</td>
<td>See Online Data Supplements 1, 2, 18-20.</td>
</tr>
</tbody>
</table>
valsartan/sacubitril, with enalapril in symptomatic patients with HFrEF tolerating an adequate dose of either ACE inhibitor or ARB, the ARNI reduced the composite endpoint of cardiovascular death or HF hospitalization significantly, by 20% (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.

<table>
<thead>
<tr>
<th>I</th>
<th>ACE: A</th>
<th>The use of ACE inhibitors is beneficial for patients with prior or current symptoms of chronic HFrEF to reduce morbidity and mortality (9-14, 25).</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>ACE inhibitors have been shown in large RCTs to reduce morbidity and mortality in patients with HFrEF with mild, moderate, or severe symptoms of HF, with or without coronary artery disease (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 (&gt;5.0 mEq/L). Angioedema occurs in &lt;1% of patients who take an ACE inhibitor, but it occurs more frequently in blacks and women (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 HFrEF 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.</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>I</th>
<th>ARB: A</th>
<th>The use of ARBs to reduce morbidity and mortality is recommended in patients with prior or current symptoms of chronic HFrEF who are intolerant to ACE inhibitors because of cough or angioedema (15-18, 27, 28).</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>ARBs have been shown to reduce mortality and HF hospitalizations in patients with HFrEF in large RCTs (15-18). Long-term therapy with ARBs in patients with HFrEF produces hemodynamic, neurohormonal, and clinical effects consistent with those expected after interference with the renin-angiotensin system (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...</td>
</tr>
</tbody>
</table>
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.

<table>
<thead>
<tr>
<th>I</th>
<th>ARNI: B-R</th>
</tr>
</thead>
<tbody>
<tr>
<td>In patients with chronic symptomatic HF/LNYHA class II or III who tolerate an ACE inhibitor or ARB, replacement by an ARNI is recommended to further reduce morbidity and mortality (19).</td>
<td></td>
</tr>
</tbody>
</table>

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/LNYHA 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).

<table>
<thead>
<tr>
<th>III: Harm</th>
<th>B-R</th>
</tr>
</thead>
<tbody>
<tr>
<td>ARNI should not be administered concomitantly with ACE inhibitors or within 36 hours of the last dose of an ACE inhibitor (31, 32).</td>
<td></td>
</tr>
</tbody>
</table>

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,
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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.

### Harm

<table>
<thead>
<tr>
<th>C-EO</th>
<th>ARNI should not be administered to patients with a history of angioedema.</th>
</tr>
</thead>
</table>

Omapatrilat, a neprilysin inhibitor (as well as an ACE inhibitor and aminopeptidase P inhibitor), was associated with a higher frequency of angioedema than that seen with enalapril in an RCT of patients with HFrEF (31). In a very large RCT of hypertensive patients, omapatrilat 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 HFrEF (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.000000000000435/-/DC2) for evidence supporting this recommendation.

**Ivabradine can be beneficial to reduce HF hospitalization for patients with symptomatic (NYHA class II-III) stable chronic HFrEF (LVEF ≤35%) who are receiving GDEM, including a beta blocker at maximum tolerated dose, and who are in sinus rhythm with a heart rate of 70 bpm or greater at rest (37-40).**

<table>
<thead>
<tr>
<th>COR</th>
<th>LOE</th>
<th>Recommendation</th>
</tr>
</thead>
<tbody>
<tr>
<td>IIa</td>
<td>B-R</td>
<td>Ivabradine can be beneficial to reduce HF hospitalization for patients with symptomatic (NYHA class II-III) stable chronic HFrEF (LVEF ≤35%) who are receiving GDEM, including a beta blocker at maximum tolerated dose, and who are in sinus rhythm with a heart rate of 70 bpm or greater at rest (37-40).</td>
</tr>
</tbody>
</table>

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 HFrEF (NYHA class II-IV, albeit with only a modest representation of NYHA class IV HF) and left ventricular ejection fraction (LVEF) ≤35%, in sinus rhythm with a resting heart rate of ≥70 beats per minute. Patients enrolled included a small number with paroxysmal atrial fibrillation (<40% of the time) but otherwise in
sinus rhythm and a small number experiencing ventricular pacing but with a predominant sinus rhythm. Those with a myocardial infarction within the preceding 2 months were excluded. Patients enrolled had been hospitalized for HF in the preceding 12 months and were on stable GDEM for 4 weeks before initiation of ivabradine therapy. The target of ivabradine is heart rate slowing (the presumed benefit of action), but only 25% of patients studied were on optimal doses of beta-blocker therapy (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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Key Words: AHA Scientific Statements; ■ Heart Failure ■ Focused Update ■ Angiotensin Receptor-Nephrilysin Inhibitor ■ Ivabradine ■ Angiotensin Receptor Blockers ■ Angiotensin-Converting Enzyme Inhibitors ■ Beta blockers ■ Angioedema ■ Natriuretic Peptides
References


### 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)

<table>
<thead>
<tr>
<th>Committee Member</th>
<th>Employment</th>
<th>Consultant</th>
<th>Speakers Bureau</th>
<th>Ownership/Partnership/Principal</th>
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<th>Institutional, Organizational, or Other Financial Benefit</th>
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### Yancy CW, et al

**Heart Failure Focused Update on Pharmacological Therapy**

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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.

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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)

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<td>Akshay S. Desai</td>
<td>Official Reviewer—HFSA</td>
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<td>Dipti Itchhaporia</td>
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<td>St Vincent Heart Center of Indiana—Medical Director, Heart Failure and Cardiac Transplantation</td>
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Yancy CW, et al  
**Heart Failure Focused Update on Pharmacological Therapy**

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<td>Judith E. Mitchell</td>
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<td>Sean P. Pinney</td>
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<td>Randall C. Starling</td>
<td>Content Reviewer—ACC Heart Failure and Transplant Council</td>
<td>Cleveland Clinic Department of Cardiovascular Medicine—Vice Chairman, Department of Cardiovascular Medicine; Section Head, Heart Failure &amp; Cardiac Transplant</td>
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| 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 |

| 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 |

*Significant relationship.
†No financial benefit.

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.
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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<td>Donald E. Casey, Jr</td>
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<td>University of Michigan—Associate Professor of Medicine, Cardiology</td>
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<td>Mark H. Drazner</td>
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<td>Gerasimos S. Filippatos</td>
<td>National and Kapodistrian University of Athens; Attikon University Hospital, Department of Cardiology, Heart Failure Unit—Professor of Cardiology</td>
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<td>Gregg C. Fonarow</td>
<td>Ahmanson-UCLA Cardiomyopathy Center—Director; UCLA Division of Cardiology—Co-Chief</td>
<td>Amgen&lt;br&gt;Janssen Pharmaceuticals&lt;br&gt;Medtronic&lt;br&gt;Novartis*</td>
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<td>• Medtronic–IMPROVE-HF (Steering Committee)†&lt;br&gt;• NHLBI*&lt;br&gt;• NIH/NIAID*&lt;br&gt;• Novartis*&lt;br&gt;• ACC/AHA Task Force on Data Standards†&lt;br&gt;• ACC/AHA Task Force on Performance Measures (Chair-Elect)†&lt;br&gt;• ACTION Registry GWTG Steering Committee (Chair)†&lt;br&gt;• AHA Consumer Health</td>
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<td>Quality Coordinating Committee†</td>
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<td>JAMA Cardiology (Associate Editor)†</td>
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<td>Michael M. Givertz</td>
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<td>Steven M. Hollenberg</td>
<td>Cooper University Hospital—Director, Coronary Care Unit, Professor of Medicine</td>
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<td>JoAnn Lindenfeld</td>
<td>Vanderbilt Heart and Vascular Institute—Director, Advanced Heart Failure and Transplant Section—Professor of Medicine</td>
<td>Abbott, Boston Scientific, Cardiometrics*, CVRx, Janssen Pharmaceuticals, Novartis, Relypsa*, RESMED*</td>
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<td>Frederick A. Masoudi</td>
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<td>ABIM</td>
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<th>Lynne W. Stevenson</th>
<th>Brigham and Women’s Hospital Cardiovascular Division—Director, Cardiomyopathy and Heart Failure Program</th>
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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](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, Health 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.
# Data Supplement 1. RCTs Comparing ARNI (Section 7.3.2.10)

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<tr>
<th>Study Acronym; Author; Year Published</th>
<th>Aim of Study; Study Type; Study Size (N)</th>
<th>Patient Population</th>
<th>Study Intervention (# patients) / Study Comparator (# patients)</th>
<th>Endpoint Results (Absolute Event Rates, P values; OR or RR; &amp; 95% CI)</th>
<th>Relevant 2° Endpoint (if any); Study Limitations; Adverse Events</th>
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<td>PARAMOUNT Solomon et al. 2012 (1) 22932717</td>
<td>Aim: To address safety and efficacy of LCZ696 (ARNI) in pts with HFrEF</td>
<td>Inclusion criteria: Pts ≥40 y of age, LVEF ≥45%, NYHA class II-III HF, NT-pro BNP &gt;400 pg/mL.</td>
<td>Intervention: LCZ696 (149) target dose 200 mg BID achieved in 81%</td>
<td>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)</td>
<td>• 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).</td>
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| PARADIGM-HF  
McMurray et al.  
2014  
(2)  
25176015 | Aim:  
To compare survival rates with the use of LCZ696 with enalapril in HF | **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. | **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) |  
15% in LCZ696 vs. 20% in valsartan group  
outcomes. Further studies needed to assess safety and efficacy in HFP EF pts. |

**Exclusion criteria:**  
Symptomatic hypotension, SBP <95 mm Hg, eGFR <30 mL/min/min/1.73m² of body surface area, serum K level >5.2 mmol/L, angioedema history, unacceptable side effects of ACE inhibitors or ARBs

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; HFrEF, 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)

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<th>Study Acronym; Author; Year Published</th>
<th>Aim of Study; Study Type; Study Size (N)</th>
<th>Patient Population</th>
<th>Study Intervention (# patients) / Study Comparator (# patients)</th>
<th>Endpoint Results (Absolute Event Rates, P values; OR or RR; &amp; 95% CI)</th>
<th>Relevant 2° Endpoint (if any); Study Limitations; Adverse Events</th>
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| ONTARGET Investigators et al. 2008   | Aim: Compare ACE (ramipril), ARB (telmisartan), and combination ACE/ARB in pts with CVD or high-risk DM | 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 |
| TRANSCEED Yusuf et al. 2008  
(4) 10757085 | 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 medications 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

**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 yr, 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

**Aim:** To investigate the effect of spironolactone on morality 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, cardiovascular disease; 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)

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<tr>
<th>Study Acronym; Author; Year Published</th>
<th>Aim of Study; Study Type; Study Size (N)</th>
<th>Patient Population</th>
<th>Study Intervention (# patients) / Study Comparator (# patients)</th>
<th>Endpoint Results (Absolute Event Rates, P values; OR or RR; &amp; 95% CI)</th>
<th>Relevant 2° Endpoint; Study Limitations; Adverse Events</th>
</tr>
</thead>
</table>
| 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 <3.0x10^9/L, neutrophils <1.5x10^9/L, or platelets <120x10^9/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 comorbidty 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:**  
- Pts included in previous RCTs of omapatrilat | 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%) | 2° endpoint:  
- 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.
<table>
<thead>
<tr>
<th>Study type: Double blind RCT</th>
<th>Size: 5,770 pts</th>
<th>Study type: Double blind RCT</th>
<th>Size: 25,302 pts</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Inclusion criteria:</strong></td>
<td><strong>Intervention:</strong> Omapatrilat target dose 80 mg daily</td>
<td><strong>Comparator:</strong> Enalapril target dose 40 mg daily</td>
<td><strong>1° endpoints:</strong> • Reduction in SBP at wk 8 • Need for new adjunctive antihypertensive therapy by wk 24</td>
</tr>
<tr>
<td>• Surgically correctable or reversible cause of HF</td>
<td>mg BID achieved 86.4% CI: 0.86–1.03; p=0.187)</td>
<td>• More frequent angioedema with omapatrilat (0.8% vs. 0.5%)</td>
<td><strong>2° endpoints:</strong> • Reduction in DBP at wk 8 • Reduction in SBP and DBP at wk 24 • BP control (SBP &lt;140 mm Hg and DBP &lt;90 mm Hg) at wk 8 and 24</td>
</tr>
<tr>
<td>• Likely to receive cardiac transplant or left ventricular assist device</td>
<td>• • Severe 1° pulmonary, renal, or hepatic disease</td>
<td>• Exclusion criteria: • Contraindication to therapy with ACE inhibitors or angiotensin II receptor antagonists</td>
<td><strong>Comments:</strong> • Greater reductions in BP in omapatrilat within each study (p&lt;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</td>
</tr>
<tr>
<td>• Severe 1° pulmonary, renal, or hepatic disease</td>
<td>• Hx of intolerance to ACE inhibitors</td>
<td>• • ACS within 1 mo</td>
<td>• Hx of intolerance to ACE inhibitors or angiotensin II receptor antagonists</td>
</tr>
<tr>
<td>• Coronary revascularization or an acute cerebral ischemic event within 3 mo</td>
<td>• 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</td>
<td>• SBP &gt;180 or &lt;90 mm Hg</td>
<td>• Hx of angioedema, anaphylaxis, drug-induced or chronic urticarial, or multiple drug sensitivities</td>
</tr>
<tr>
<td>• 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</td>
<td>• Intravenous positive inotropic agent within 2 wk</td>
<td>• Heart rate &gt;130 bpm</td>
<td>• Recent hospitalization for MI, unstable angina, stroke, TIA or COPD</td>
</tr>
<tr>
<td>• Hx or hospitalization or intravenous therapy for HF within 48 h</td>
<td>• SBP &gt;180 or &lt;90 mm Hg</td>
<td>• Serum creatinine &gt;2.5 mg/dL</td>
<td>• Recent treatment for malignancy, chronic renal</td>
</tr>
<tr>
<td>• Intravenous positive inotropic agent within 2 wk</td>
<td>• Serum potassium &lt;3.5 or &gt;5.2 mmol/L</td>
<td>• <strong>Exclusion criteria:</strong></td>
<td></td>
</tr>
<tr>
<td>• SBP &gt;180 or &lt;90 mm Hg</td>
<td></td>
<td>• Contraindication to therapy with ACE inhibitors or angiotensin II receptor antagonists</td>
<td></td>
</tr>
<tr>
<td>• Heart rate &gt;130 bpm</td>
<td></td>
<td>• Hx of angioedema, anaphylaxis, drug-induced or chronic urticarial, or multiple drug sensitivities</td>
<td></td>
</tr>
<tr>
<td>• Serum creatinine &gt;2.5 mg/dL</td>
<td></td>
<td>• Recent hospitalization for MI, unstable angina, stroke, TIA or COPD</td>
<td></td>
</tr>
<tr>
<td>• Serum potassium &lt;3.5 or &gt;5.2 mmol/L</td>
<td></td>
<td>• Recent treatment for malignancy, chronic renal</td>
<td>OCTAVE Kostis et al. 2004 (10) 14751650</td>
</tr>
</tbody>
</table>
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 HFrEF (Section 7.3.2.11)

<table>
<thead>
<tr>
<th>Study Acronym; Author; Year Published</th>
<th>Aim of Study; Study Type; Study Size (N)</th>
<th>Patient Population</th>
<th>Study Intervention (# patients) / Study Comparator (# patients)</th>
<th>Endpoint Results (Absolute Event Rates, P values; OR or RR; &amp; 95% CI)</th>
<th>Relevant 2° Endpoint (if any); Study Limitations; Adverse Events</th>
</tr>
</thead>
</table>
| 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  

**1° endpoint:**  
- 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  

**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 mc mol /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).
| BEAUTIFUL | Aim: Assess the mortality-morbidity benefits of Ivabradine in pts with CAD and LV systolic dysfunction | 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. | 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:  
- 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 If 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 If Inhibitor Ivabradine in Patients with Coronary Artery Disease; SHIFT, Systolic Heart Failure Treatment with the If 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.
<table>
<thead>
<tr>
<th>Study Name, Author, Year</th>
<th>Aim of Study</th>
<th>Study Type</th>
<th>Background</th>
<th>Study Size</th>
<th>Patient Population</th>
<th>Endpoints</th>
<th>Mortality</th>
<th>Trial Duration (Years)</th>
<th>Absolute Benefit</th>
<th>P Values &amp; 95% CI:</th>
</tr>
</thead>
<tbody>
<tr>
<td>CONSENSUS 1987</td>
<td>To Evaluate influence of enalapril on prognosis of NYHA class IV HF</td>
<td>RCT</td>
<td>Diuretics (spironolactone 53%, mean dose 80mg), digitalis (93%), other vasodilators, except ACEI (ie, nitrates 46%)</td>
<td>253; 127;126</td>
<td>CAD 73%</td>
<td>APE; hemodynamically important aortic/MV stenosis; MI w/in prior 2 mo Unstable angina; planned cardiac surgery; right HF b/c of pulm disease; Cr &gt;300 mmol/L</td>
<td>Mortality</td>
<td>Change in NYHA-FC, LV size, Cr level</td>
<td>52% placebo group and 36% enalapril group (6 mo mortality: 26% in enalpril group and 44% in placebo group)</td>
<td>0.51 y</td>
</tr>
<tr>
<td>10 y FU of CONSENSUS 1999</td>
<td>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).</td>
<td>10-y open-label follow-up study (via completion of a questionnaire) on the survival status of pts in CONSENSUS-a RCT.</td>
<td>315; 77; 58</td>
<td>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</td>
<td>Mortality</td>
<td></td>
<td>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</td>
<td>10 y</td>
<td>5</td>
<td></td>
</tr>
<tr>
<td>SOLVD 1991</td>
<td>Study the effect of enalapril on mortality and hospitalization in pts with chronic HF and EF &lt;35%</td>
<td>RCT</td>
<td>Diuretics + Digoxin</td>
<td>2569; 1289, 1284</td>
<td>Ischemic heart disease 72%</td>
<td>LVEF &lt;35%; Mild to severe (11% class IV=2% class IV); LVEF 25%; BP; 125/77; HR: 80; AF: 8-12%</td>
<td>Mortality</td>
<td>Hospitalizations; Incidence of MI; Mortality by specific causes; Combined mortality and morbidity from both SOLVD+SOLVD-2.10%</td>
<td>Treating 1000 SOLVD+ pts with enalapril for ~3 y would save ~50 premature deaths and 350 hospitalizations.</td>
<td>3.45 y</td>
</tr>
</tbody>
</table>
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%.

**SOLVD**

*1463530 (18)*

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.

**SOLVD F/U 2003**

*12789569 (19)*

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.

**ATLAS**

*10587334 (20)*

To test the hypothesis that the long-term administration of captopril to survivors of an acute coronary ischemic event or revascularization procedure within 2 mo; History of sustained or symptomatic ventricular tachycardia; Intolerant of ACEIs; ScI >2.5 mg/dL

<table>
<thead>
<tr>
<th>Post-MI ACEI Use</th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>SAVE, 1992</td>
<td>1386652 (21)</td>
<td>To test the hypothesis that the long-term administration of captopril to survivors of an acute coronary ischemic event or revascularization procedure within 2 mo; History of sustained or symptomatic ventricular tachycardia; Intolerant of ACEIs; ScI &gt;2.5 mg/dL</td>
<td>3.5 y</td>
</tr>
</tbody>
</table>

© 2016 American College of Cardiology Foundation and American Heart Association, Inc.
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.

**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 18%; 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 or 2 cardiac enzymes; LV dysfunction (EF <35%); NYHA class I - 43%; 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 thetrandolapril 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 withtrandolapril 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; CW, 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)**

<table>
<thead>
<tr>
<th>Study Name, Author, Year</th>
<th>Aim of Study</th>
<th>Study Type</th>
<th>Background Therapy</th>
<th>Study Size</th>
<th>Etiology</th>
<th>Patient Population</th>
<th>Severity</th>
<th>Endpoints</th>
<th>Mortality</th>
<th>Trial Duration (Y)</th>
<th>Statistical Results</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>CHARM-Alternative: Granger et al; (2003) 13678970 (24)</strong></td>
<td>Discover whether ARB could improve outcome in pts not taking an ACEI (intolerant)</td>
<td>RCT</td>
<td>Diuretics, Beta-blockers (55%), spironolactone (24%),Digoxin 45-46%</td>
<td>2548; 1276; 1272</td>
<td>Ischemic 62-69%</td>
<td>Symptomatic HF; EF &lt;40%, no ACEI (bias of intolerance)</td>
<td>NYHA II IV; mild to severe (&lt;4% class IV); EF: 30%; BP: 110/70; HR: 74-75; AF: 25-26%</td>
<td>Composite of CV death or hospital admission for CHF</td>
<td>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</td>
<td>2.8 y</td>
<td>Absolute reduction of 7 major events per 100 pts treated - NNT 14 pts to prevent 1 CV death or hospitalization. HR: 0.77 (95% CI: 0.67-0.89); p=0.0004</td>
</tr>
<tr>
<td><strong>CHARM-Added: McMurray et al; (2003) 13678969 (25)</strong></td>
<td>To investigate whether ARB + ACEI in pts with chronic HF improve clinical outcomes</td>
<td>RCT</td>
<td>Beta blocker-55%, spironolactone (17%),Digoxin 58-59%</td>
<td>14,703; 2499</td>
<td>Ischemic 67-70%</td>
<td>Symptomatic HF; EF &lt;40%; Treatment with ACEI; Age &lt;18 y</td>
<td>NYHA class II IV; mild to severe (&lt;3% class IV); EF: 28%; BP: 125/75; HR: 74; AF: 27%</td>
<td>Composite of CV death or hospital admission for CHF</td>
<td>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</td>
<td>3.4 y</td>
<td>Absolute reduction of 4.4 pts with events per 100 pts treated - NNT 14 pts to prevent 1 first event of CV death or CHF hospitalization. RR: 0.85 (95% CI: 0.75-0.96); p=0.011</td>
</tr>
<tr>
<td><strong>VALIANT: Pfeffer et al; (2003) 14010150 (26)</strong></td>
<td>Compare the effect of an ARB, ACEI and the combination of the 2 on mortality</td>
<td>Randomize d double blind multicenter trial</td>
<td>Beta-blockers, ASA 490, Captopril 490 VAL + CAP: 4895</td>
<td>14,703; Valasartan 490</td>
<td>Ischemic 100% (MI inclusion criteria)</td>
<td>Age &lt;18 y; Acute MI complicated by HF; LV systolic dysfunction (EF &lt;35%); (&lt;40% on radionuclide ventriculography); SBP &gt;100 mmHg; Cr &gt;2.5 mg/dL</td>
<td>NYHA IV, asymptomatic-severe; EF 35%; BP: 123/72; HR: 76</td>
<td>Death from any cause</td>
<td>Death (any cause); New CV death, hospital admission, nonfatal MI, nonfatal stroke, coronary revascularization; Death (any cause): New DM</td>
<td>12.5% VAL; 12.3% VAL + CAP; 12.2% CAP</td>
<td>2.1 y</td>
</tr>
<tr>
<td><strong>Val-HeFT: Cohn et al. (2001) 11706945 (27)</strong></td>
<td>Evaluate long term effects of adding ARB to standard therapy for HF</td>
<td>RCT</td>
<td>Diuretics; Digoxin 67%; Beta blocker 35%; ACEI 51%</td>
<td>5010; 2511; 2499</td>
<td>Ischemic 57%</td>
<td>Age &lt;18 y; NYHA II, IV; At least 2 wk of background meds including ACEIs; EF &lt;40% and LVID &gt;2.9 cm/BSA</td>
<td>NYHA II, IV (only ~2% class IV); Mild to severe; EF 27%; BP: 123/76; AF: 12%</td>
<td>Mortality; Combined endpoint of mortality and morbidity</td>
<td>Change in EF; • NYHA class, QOL scores; Signs and symptoms of HF</td>
<td>1.92 y</td>
<td>Mortality similar for the 2 treatment groups. RR: 0.87; 97.5% CI, 0.77-0.97; p=0.009</td>
</tr>
<tr>
<td><strong>HEAL study; Lancet 2009; 374(9682): 1840-48. 19229955 (28)</strong></td>
<td>Compared the effects of high-dose vs low-dose losartan on clinical outcomes in pts with HF.</td>
<td>RCT</td>
<td>Diuretic drugs (77%), beta blockers (72%), and ARBs (36%)</td>
<td>3846; losartan 150 mg (n=1927) or 50 mg daily (n=1919).</td>
<td>Ischemic 64%</td>
<td>Age &lt;18 y; NYHA class II IV; LVEF &lt;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</td>
<td>NYHA IV (79%); EF: 33%; BP: 124/77; HR: 71; AF: 28%</td>
<td>Death or admission for HF</td>
<td>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</td>
<td>4.3 y median IU</td>
<td>Treating pts with 150 mg dose instead of 50 mg dose would result in 1 additional pt with the primary event at 4 y for every 31 pts treated. Composite: 428 (43%) pts in 150 mg group vs. 389 (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 490 vs. 503 pts admitted for HF (0.78, 0.78-0.98; p=0.025)</td>
</tr>
</tbody>
</table>
### 2013 HF Guideline Data Supplement 20. Beta Blockers (Section 7.3.2.4)

<table>
<thead>
<tr>
<th>Study Name, Author, Year</th>
<th>Aim of Study</th>
<th>Study Type</th>
<th>Background Therapy</th>
<th>Study Size</th>
<th>Etiology</th>
<th>Patient Population</th>
<th>Severity</th>
<th>Endpoints</th>
<th>Mortality</th>
<th>Trial Duration</th>
<th>Statistical Results</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>CIBIS II CIBIS</strong> 8 investigators and committee members (1999) <a href="30">1032943</a></td>
<td>Investigate the efficacy of bisoprolol in decreasing all-cause mortality in chronic HF</td>
<td>RCT - multicenter double-blind randomised placebo controlled trial (Europe)</td>
<td>Diuretics + ACEI; [amiodarone allowed-14-16%]</td>
<td>2647; 1327; 1230</td>
<td>Documented ischaemic heart disease 50%</td>
<td>NYHA class II or IV EF: &lt;35% 18-80 y old</td>
<td>Uncontrolled HTN; MRAH with previous 3 mo; PTCA/CABG with previous 6 mo; AV-block &gt;1st degree w/o PPM; Heart rate &lt;60 bpm; resting SBP &lt;100mmHg; renal failure; Reversible obstruct lung disease; Use of beta blocker</td>
<td>Moderate to severe. Mean BP: 130/80; Mean EF: 28%; Mean LVEFF: 6.7 cm; AF: 29%</td>
<td>All-cause mortality</td>
<td>All-cause hospital admissions</td>
<td>15.2% Placebo group 8.8% Treatm’t group</td>
</tr>
<tr>
<td>**MERIT-HF; MERIT study Group; (1999) <a href="31">10376614</a></td>
<td>Investigate whether Metoprolol CR/XL lowered mortality in pts with decreased EF and symptoms of HF</td>
<td>RCT - multicenter double-blind randomised placebo controlled trial (Europe + USA)</td>
<td>Diuretics + ACEI [Amiodarone NOT allowed]</td>
<td>3991; 1991; 2001</td>
<td>Ischaemic 65%</td>
<td>NYHA II-IV; 40-80 y old; LVEF &lt;40% (36-40 if 5-min walk &lt;450m); heart rate &gt;88 bpm</td>
<td>MRAH with 28; Contra-indication or current use of beta blocker; PTCA/CABG with 4 mo Planned transplant or ICD; Heart block &gt;1st degree w/o PPM; SBP &lt;100 mmHg</td>
<td>Mild to severe. Mean BP: 130/78; Mean EF: 28%; AF 16-17%</td>
<td>All-cause mortality</td>
<td>All-cause mortality in combination with all-cause admission to hospital</td>
<td>N/A</td>
</tr>
<tr>
<td><strong>CHARM-Overall</strong> 10376614 (20)</td>
<td>Aimed to find out whether the use of an ARB could reduce mortality and morbidity.</td>
<td>RCT - parallel, randomized double-blind,</td>
<td>Diuretics 83% Beta blockers 55% ACEI 43%</td>
<td>7601 pts</td>
<td>NYHA class II-IV for at least 4 wk; 3 distinct populations: pts with LVEF &lt;40% who were not receiving ACEIs (previous intolerance) or who were currently receiving ACE, and pts with LVEF &gt;40%</td>
<td>Scr &gt; 265 mcml/l, serum potassium &gt;5.5 mmol/l. Bilateral renal artery stenosis; Symptomatic hypertension 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</td>
<td>NYHA IV NYHA IV-IV Only 3% class IV</td>
<td>The primary outcome of the overall program: all-cause mortality. For all the component trials: CV death or hospital admission for CHF.</td>
<td>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.</td>
<td>3.1 y</td>
<td>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% CI: 0.82-0.99; p=0.032)</td>
</tr>
</tbody>
</table>
**COPERNICUS**; Packer et al; (2002) 11396947 (32)

Investigate whether Carvedilol is beneficial in severe HF.

- **RCT—double blind**
- Diuretics (PO or IV) + ACEI (or ARB); [Amiodarone allowed 17-18%]
- Euvolumic NYHA class IV; LVEF <25%
- No positive inotropic or vasoactive agents win 4 d
- Pt requiring hospitalized intensive care; Use of positive inotropes or IV; vasoactive agents win 4 d
- Coronary revascularization/MICVA; sign VT or VF win 2 mo; SBP < 85 mmHg; Heart rate <60; Cr >2.0 mg/dL
- Severe Mean BP: 123/76; Mean HR: 82; 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; (2002) 15642700 (33)

Assess effects of the beta blocker Nebivolol in pts >70 y regardless of EF.

- **RCT**
- Diuretics + ACEI (+aldosterone antagonist in 29%)
- Prior h/o CAD in 69%
- Age >70 CHF with 1 of the following: hospitalization with CHF win 1 year or EF <35% win the past 6 mo
- New HF therapy win 6 wk or change in drug therapy win 2 wk
- Contractindation to beta blockers, current use of beta blockers Significant renal dysfunction: CVA with 3 mo.
- Mild to severe Mean BP: 139/81; Mean HR: 79; Mean EF 36% (13 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
- CV hospital admissions
- NYHA class assessment; 6 MWT
- N/A
- 1.75 y
- Absolute risk reduction 4.2%; 24 pts would need to be treated for 1 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 11386364 (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%].
- 2108; 1354; 1354
- Ischemic heart disease: 29% of pts with severe HF: 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 <60mmHg
- Decompensated HF.
- NYHA II or IV (92% class II) 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 or 15% in the bucindolol group.
- N/A
- ~2 y
- 449 pt in placebo group (33%) died; 411 in the bucindolol group (38%; HR: 0.80; 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; 1518 carvedilol; 1518 metoprolol tartrate
- N/A
- NYHA class IV HF 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
- 4.8 y
- All-cause mortality 34% carvedilol and 40% metoprolol (HR: 0.83; 95% CI 0.74-0.93; p=0.0017)
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%; 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 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

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

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.