# 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)

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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>
</tr>
</thead>
<tbody>
<tr>
<td>PARAMOUNT Solomon et al. 2012 (1) 22932717</td>
<td>Aim: To address safety and efficacy of LCZ696 (ARNI) in pts with HFpEF</td>
<td>Inclusion criteria: Pts ≥40 y of age, LVEF ≥45%, NYHA class II–III HF, NT-pro BNP &gt;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.</td>
<td>Intervention: LCZ696 (149) target dose 200 mg BID achieved in 81% Comparator: Valsartan (152) target dose 160 mg BID achieved in 78%</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) 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...</td>
<td></td>
</tr>
</tbody>
</table>

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| PARADIGM-HF | 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) | outcomes. Further studies needed to assess safety and efficacy in HFp EF pts. |

<p>| Study type: RCT | Size: 8,442 | | 15% in LCZ696 vs. 20% in valsartan group | 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; HFpEF, 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. |</p>
<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>
| 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) 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)  
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)*  
**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.  
**RALES**  
*Pitt et al. 1999 (7)*  
**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, 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.

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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)

<table>
<thead>
<tr>
<th>Study Acronym</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       | Determine if inhibition of neutral endopeptidase and ACE with the vasopeptidase inhibitor omapatrilat is better than ACE inhibition alone with lisinopril | 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  
  | 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  
  | 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      | 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  
  | Intervention: Omapatrilat (2,886), target dose 40 mg daily  
  Comparator: Enalapril (2,884) target dose 10  
  | 1° endpoint: Combined risk of death or hospitalization for HF requiring IV treatment  
  | 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.  
  | Comments:  
  - No significant difference HR: 0.94 (95%)  
<p>|</p>
<table>
<thead>
<tr>
<th>Study type: Double blind RCT</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Size:</strong> 5,770 pts</td>
</tr>
<tr>
<td>Inclusion criteria:</td>
</tr>
<tr>
<td>• Surgically correctable or reversible cause of HF</td>
</tr>
<tr>
<td>• Likely to receive cardiac transplant or left ventricular assist device</td>
</tr>
<tr>
<td>• Severe 1° pulmonary, renal, or hepatic disease</td>
</tr>
<tr>
<td>• Hx of intolerance to ACE inhibitors</td>
</tr>
<tr>
<td>• ACS within 1 mo</td>
</tr>
<tr>
<td>• Coronary revascularization or an acute cerebral ischemic event within 3 mo</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>
</tr>
<tr>
<td>• Hx or hospitalization or intravenous therapy for HF within 48 h</td>
</tr>
<tr>
<td>• Intravenous positive inotropic agent within 2 wk</td>
</tr>
<tr>
<td>• SBP &gt;180 or &lt;90 mm Hg</td>
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<tr>
<td>• Heart rate &gt;130 bpm</td>
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<tr>
<td>• Serum creatinine &gt;2.5 mg/dL</td>
</tr>
<tr>
<td>• Serum potassium &lt;3.5 or &gt;5.2 mmol/L</td>
</tr>
<tr>
<td>mg BID achieved 86.4% CI: 0.86–1.03; p=0.187</td>
</tr>
<tr>
<td>More frequent angioedema with omapatrilat (0.8% vs. 0.5%)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>OCTAVE Kostis et al. 2004 (10) 14751650</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Aim:</strong> Compare safety and efficacy of dual ACE and NEP inhibitors to ACE inhibitors alone</td>
</tr>
<tr>
<td><strong>Study type:</strong> Double blind RCT</td>
</tr>
<tr>
<td><strong>Size:</strong> 25,302 pts</td>
</tr>
<tr>
<td>Inclusion criteria:</td>
</tr>
<tr>
<td>• Age ≥18</td>
</tr>
<tr>
<td>• 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 &lt;100 mm Hg, or trough DBP 90–99 mm Hg and SBP &lt;160 mm Hg); Group 3 hypertension with persistent moderate to severe hypertension (trough SBP 160–179 mm Hg and DBP &lt;110 mm Hg, or trough DBP 100–109 mm Hg and SBP &lt;180 mm Hg)</td>
</tr>
<tr>
<td>Comparator: Omapatrilat target dose 80 mg daily</td>
</tr>
<tr>
<td>Intervention:</td>
</tr>
<tr>
<td>• Reduction in SBP at wk 8</td>
</tr>
<tr>
<td>• Need for new adjunctive antihypertensive therapy by wk 24</td>
</tr>
<tr>
<td>Comparator: Enalapril target dose 40 mg daily</td>
</tr>
<tr>
<td>1st endpoints:</td>
</tr>
<tr>
<td>2nd endpoints:</td>
</tr>
<tr>
<td>Greater reductions in BP in omapatrilat within each study (p&lt;0.001)</td>
</tr>
<tr>
<td>Overall mean reduction in SBP ≥3.6 mm Hg</td>
</tr>
<tr>
<td>Larger reductions in BP in black pts with omapatrilat than with enalapril. But overall reduction smaller with both drugs than in other subgroups.</td>
</tr>
<tr>
<td>Adverse events, serious adverse events, and deaths were the same for omapatrilat and enalapril</td>
</tr>
</tbody>
</table>

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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. | **Inclusion criteria:** Pts ≥18 y of age in sinus rhythm, heart rate at rest ≥70 bpm, MTD for HF med | **Intervention:** Ivabradine | **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 | Aim: To assess the effect of heart rate reduction by the selective sinus-node inhibitor ivabradine on outcomes in HF | **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 |

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<table>
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<tr>
<th>Study</th>
<th>Aim</th>
<th>Inclusion criteria</th>
<th>Intervention</th>
<th>1st endpoint</th>
<th>Adverse Effects</th>
</tr>
</thead>
<tbody>
<tr>
<td>SIGNIFY</td>
<td>Assess the mortality-morbidity benefits of ivabradine in pts with stable CAD without clinical HF</td>
<td>Stable CAD without clinical HF and heart rate of ≥70 bpm and in sinus rhythm, persistence and confirmation of ≥1 CV risk factors</td>
<td>Ivabradine (n=9,550)</td>
<td>• Composite of CV death and nonfatal MI</td>
<td>• Adverse Events: Increased bradycardia, AF, phosphenes and cardiac disorders.</td>
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<td>Exclusion criteria: Serum creatinine &gt;200 mcmol /L, significant anemia, ALT or AST &gt;3 times upper normal value, unstable CV condition, LVEF ≤40%; MI, coronary revascularization, stroke ≤3 mo.</td>
<td>Comparator: Placebo (n=9,552)</td>
<td>• Results: No significant difference in incidence of 1st 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)</td>
<td>• Significant interaction between ivabradine and presence of angina in a subgroup analysis (p=0.02).</td>
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<td>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</td>
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<td>• Hospitalization for worsening HF: ivabradine better. 16% vs 21%, HR: 0.74 (95% CI: 0.66–0.83; p&lt;0.001)</td>
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<td>• Death from HF: ivabradine better. 3% vs. 5%; HF: 0.74 (0.58–0.94); p=0.014</td>
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<td>• Ivabradine better for all-cause hospitalization, HF hospitalization, CV hospitalization, and composite 2° endpoint</td>
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<td>• Analyzed as time to first event. Median follow-up of 22.9 mo</td>
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<td>• In subgroup analysis, effect limited to those with higher baseline heart rate (≥77 bpm)</td>
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<td>• Use of devices was low (CRT in 1% and ICD in 4%)</td>
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<td>• Mean age 61 y</td>
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<td>• When added to GDEM, including beta blocker at optimal dose, ivabradine reduced adverse events, driven largely by HF mortality or HF hospitalization</td>
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<td>Adverse Effects:</td>
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<td></td>
<td></td>
<td>• 1% withdrew due to bradycardia (p&lt;0.001)</td>
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<td></td>
<td>• Phosphenes 3% (p&lt;0.001)</td>
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<td></td>
<td>• Comparable across age groups</td>
<td></td>
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<td></td>
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<td></td>
<td>• AF - ivabradine 9% vs. placebo 8%  (p=0.012)</td>
<td></td>
</tr>
</tbody>
</table>

**Notes:**
- **SIGNIFY** Fox et al. 2014 (13) 25176136
<table>
<thead>
<tr>
<th><strong>BEAUTIFUL</strong></th>
<th><strong>Aim:</strong> Assess the mortality-morbidity benefits of Ivabradine in pts with CAD and LV systolic dysfunction</th>
<th><strong>Inclusion criteria:</strong></th>
<th><strong>Intervention:</strong></th>
<th><strong>1° endpoint:</strong></th>
<th><strong>2° endpoints:</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td>Fox et al. 2008 (14)</td>
<td></td>
<td></td>
<td>Ivabradine n=5,479</td>
<td>Composite of CV death, admission for MI and admission for HF</td>
<td>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</td>
</tr>
<tr>
<td></td>
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<td></td>
<td>Placebo in addition to appropriate CV medication n=5,438</td>
<td>No difference in composite 1° endpoint (22.5% vs. 22.8%; HR: 1.00; 0.91–1.1; p=0.94)</td>
<td>No differences in any prespecified subgroup.</td>
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<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>No differences in any prespecified subgroup.</td>
<td></td>
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<td></td>
<td>No differences in 2° endpoints in overall population.</td>
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<td></td>
<td>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)</td>
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<td></td>
<td>28% in Ivabradine group discontinued medication (vs. 16%), largely due to bradycardia (13% vs. 2%)</td>
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<td>No difference in significant adverse effects (23% vs. 23%; p=0.70)</td>
</tr>
</tbody>
</table>

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.

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<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>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 283575 (15)</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>Severe HF/symptoms at rest/NYHA class IV; Increased heart size &gt;600 mL; BP: 120/75; HR: 80; AF 50%</td>
<td>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 &gt;300 mmol/L</td>
<td>Mortality</td>
<td>Change in NYHA-FC, LV size, Cr level</td>
<td>0.51 y</td>
<td>N/A</td>
</tr>
<tr>
<td>10 y FU of CONSENSUS 1999 10099910 (16)</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>All pts were offered open-label enalapril therapy</td>
<td>Mortality</td>
<td></td>
<td>10 y</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></td>
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</tr>
<tr>
<td>SOLVD 1991 2567934 (17)</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; 1285; 1284</td>
<td>Ischemic heart disease 72%</td>
<td>LVEF &lt;35%; Mild to severe (11% class I/24% class IV); LVEF 25%; BP: 125/77; HR: 80; AF: 8-12%</td>
<td>Age &gt;60 y; Unstable angina; MI w/in past mo; Cr&lt;2.0 mg/dL</td>
<td>Mortality</td>
<td>Hospitalizations; Incidence of MI; Mortality by specific causes; Combined mortality and morbidity from both SOLVD+SOLVD+</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
SOLVD 1992

Study effect of ACEIs on total mortality and mortality from CV causes, the development of HF, and hospitalization for HF in pts with EF \( \leq 35\% \). RCT

No drug treatment for HF

4228; 2111; 2117

History of ischemic heart disease 85%

EF \( \leq 35\% \), 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 hospitalization for HF

3.12 y

Reduced mortality: \( p=0.30; \) 95% CI: -8-21%

Post-MI ACEI Use

SAVE, 1992

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: 0.95 Cl: 0.84-0.95, \( p=0.0003 \).

SOLVD FU 2003

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

N/A

N/A

N/A

N/A

Mortality

N/A

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

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 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

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 \( \geq 6 \) 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 IV (mainly class II); LVEF 23%; SBP 126 mmHg; HR 80; NYHA class: II(few II and IV)

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

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 (\( p=0.002 \)).
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.

The use of an ACEIs or the need for such an agent; SG > 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

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

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 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 mmo/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 (total 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.
### 2013 HF Guideline Data Supplement 19. ARBs (Section 7.3.2.3)

<table>
<thead>
<tr>
<th>Study Name, Author, Year</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>Secondary Endpoint</th>
<th>1st Y Mortality</th>
<th>Duration (Y)</th>
<th>Statistical Results</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>CHARM-Alternative</strong>; Granger et al; (2003) 13678870 (24)</td>
<td>RCT</td>
<td>Diuretics, Beta-blockers (55%), spironolactone 24%, Digoxin 45-46%</td>
<td>14,703; 1015</td>
<td>Ischemic/ Non-Ischemic</td>
<td>Symptomatic HF, EF &lt;40, no ACEI (bic 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>
<td></td>
</tr>
<tr>
<td><strong>CHARM-A CDoE; McMurray et al; (2003) 13678869 (25)</strong></td>
<td>RCT</td>
<td>Beta blocker-55%, spironolactone 17%, Digoxin 58-59%</td>
<td>2548; 1276; 1272</td>
<td>Ischemic-62-63%</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); 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 23 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>
<td></td>
</tr>
<tr>
<td><strong>VALIANT; Pfeffer et al; (2003) 14010100 (26)</strong></td>
<td>Randomized double blind multicenter trial</td>
<td>Beta-blockers, ASA 91, Captopril; 4909 VAL + CAP: 4885</td>
<td>14,703; 4909; VAL + CAP: 4885</td>
<td>Ischemic 100% (MI inclusion criteria)</td>
<td>Age &lt;18 y; Acute MI complicated by HF, LV systolic dysfunc (EF &lt;35%), &lt;40% on radionuclide ventriculography; SBP &gt;100 mmHg; Cr &lt;2.5 mg/dL</td>
<td>NYHA III-IV; asymptomatic-severe; EF 35%; BP: 123/72; HR: 76</td>
<td>Death from any cause</td>
<td>12.5% VAL; 12.3% VAL + CAP</td>
<td>12.3% CAP</td>
<td>2.1 y</td>
<td>VAL and CAP: 1.0 (97.5% CI: 0.90-1.11); p=0.08; VAL+CAP and CAP: 0.98 (97.5% CI: 0.89-1.09); p=0.73</td>
</tr>
<tr>
<td><strong>Val-HeFT; Cohn et al; (2003) 11796645 (27)</strong></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-III, 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; 95% CI, 0.77-0.97; p=0.009</td>
<td></td>
</tr>
<tr>
<td><strong>HEACL study; Lancet; 2009; 374: 1840-48. 13622995 (28)</strong></td>
<td>RCT</td>
<td>Diuretic drugs (77%), beta blockers (72%), and ARBs (38%)</td>
<td>3846 losartan 150 mg (n=1927) or 50 mg daily (n=1219)</td>
<td>Ischemic 64%</td>
<td>Hypertension or lactation, known intolerance to ARBs; Systolic arterial blood pressure &lt;90 mm Hg; Significant stenotic valvular heart disease; Active myocarditis; active pericarditis; Planned heart transplantation within 6 mo; coronary angioplasty, CABG, acute MI, UA pectoris, cerebrovascular accident, or TIA within the previous 12 wk; Suspected significant renal</td>
<td>NYHA IV (79% I); 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, CHF admission, admission for HF, and changes in the severity of heart disease</td>
<td>4.3 y</td>
<td>median I2</td>
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</tr>
</tbody>
</table>

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### 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>Primary Endpoint</th>
<th>Secondary Endpoint</th>
<th>Mortality</th>
<th>Trial Duration</th>
<th>Statistical Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>CIBIS II CIBS II investigators and committee members (1999) 10323943 (30)</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; 1320</td>
<td>Documented ischemic 50%</td>
<td>NYHA class II or IV EF: &lt;35% 18-80 y old</td>
<td>Uncontrolled HTN; NYHA with previous 3 mo; PTC/CA/BBI with previous 6 mo; AV-block &gt;1st degree with PPM; Heart rate &lt; 60bpm; resting SBP &lt;100mmHg; renal failure; Reversible obstruct lung disease; Use of beta blocker</td>
<td>Moderate to severe.</td>
<td>All-cause mortality</td>
<td>All-cause hospital admissions</td>
<td>13.2% Placebo group 8.8% Treatm't group</td>
<td>N/A</td>
</tr>
<tr>
<td>HR: 0.66 (95% CI: 0.54-0.83); p&lt;0.0001</td>
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<tr>
<td>MERIT-HF: MERIT study Group; (1999) 10378664 (31)</td>
<td>Investigate whether Metoprolol CR/XL lowered mortality i 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; 2011</td>
<td>Ischemic 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>NYHA II-IV; NYHA with 28 5; Contra-indication or current use of beta blocker; PTC/CA/BBI with 4 mo Planned transplant or ICD; Heart block &gt;1st degree w/o PPM; SBP &lt;100mmHg</td>
<td>Mild to severe.</td>
<td>All-cause mortality</td>
<td>All-cause hospital admissions</td>
<td>11.0% Placebo group 7.3% Treatm't group</td>
<td>N/A</td>
</tr>
<tr>
<td>Treatment of 27 pt for 1 y can prevent 1 death.</td>
<td>0.66 (95% CI: 0.53-0.81); p=0.0009</td>
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</tbody>
</table>

**ACEI** indicates angiotensin-converting-enzyme inhibitor; **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; **HIO** 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; **VALIANT** Valsartan in Acute Myocardial Infarction; **Xarelto** rivaroxaban; **XO** xanthine oxidase; **XO-2** fenoldopam; **XO-1** aminophylline; **XV** xanthinophyllines; **xenon** inhaled xenon; **y** years; **z** zero.
<table>
<thead>
<tr>
<th>Study</th>
<th>Design</th>
<th>Intervention</th>
<th>Comparator</th>
<th>Main Outcome Measures</th>
<th>Key Findings</th>
</tr>
</thead>
<tbody>
<tr>
<td>SENIORS</td>
<td>RCT</td>
<td>Diuretics + ACEi (enalapril or lisinopril)</td>
<td>Placebo</td>
<td>Composite of all-cause mortality or CV hospital admission</td>
<td>Absolute risk reduction in all-cause mortality was 4.8% (HR: 0.86; 95% CI: 0.74-0.99; p&lt;0.003)</td>
</tr>
<tr>
<td>COMET</td>
<td>RCT</td>
<td>Diuretics, ACEi (enalapril or lisinopril)</td>
<td>Placebo</td>
<td>All-cause mortality</td>
<td>Absolute risk reduction in all-cause mortality was 4.8% (HR: 0.86; 95% CI: 0.74-0.99; p&lt;0.003)</td>
</tr>
<tr>
<td>RCT</td>
<td>Diuretics, ACEi (enalapril or lisinopril)</td>
<td>Placebo</td>
<td>All-cause mortality</td>
<td>Absolute risk reduction in all-cause mortality was 4.8% (HR: 0.86; 95% CI: 0.74-0.99; p&lt;0.003)</td>
<td></td>
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</table>
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, 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 SO2≥92 mmol/L AV block>1° without a functioning pacemaker Obstructive lung disease contraindicating bisoprolol treatment NYHA II or III, mild to moderate CHF LVEF <35% 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 | 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, Digitals 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.