Optimizing Heart Failure Therapy: Answers to Pivotal Questions

Juan M. Aranda, Jr., MD, FACC, FHFS
Professor of Medicine
Director of Heart Failure and Cardiac Transplantation
University of Florida College of Medicine
¿Cuántas pastillas necesitamos para insuficiencia cardiaca y cuál es la secuencia?
## Treatments That May Cause Harm in Patients with Symptomatic HFrEF

<table>
<thead>
<tr>
<th>Recommendations</th>
<th>Class</th>
<th>Level</th>
<th>Ref</th>
</tr>
</thead>
<tbody>
<tr>
<td>Thiazolidinediones (glitazones) are not recommended in patients with HF, as they increase the risk of HF worsening and HF hospitalization.</td>
<td>III</td>
<td>A</td>
<td>209, 210</td>
</tr>
<tr>
<td>NSAIDs or COX-2 inhibitors are not recommended in patients with HF, as they increase the risk of HF worsening and HF hospitalization.</td>
<td>III</td>
<td>B</td>
<td>211–213</td>
</tr>
<tr>
<td>Diltiazem or verapamil are not recommended in patients with HFrEF, as they increase the risk of HF worsening and HF hospitalization.</td>
<td>III</td>
<td>C</td>
<td>214</td>
</tr>
<tr>
<td>The addition of an ARB (or renin inhibitor) to the combination of an ACE-I and an MRA is not recommended in patients with HF, because of the increased risk of renal dysfunction and hyperkalaemia.</td>
<td>III</td>
<td>C</td>
<td></td>
</tr>
</tbody>
</table>

Recommendations for Anemia

In patients with HF and anemia, erythropoietin-stimulating agents should not be used to improve morbidity and mortality (176).

NEW: Current recommendation reflects new evidence demonstrating absence of therapeutic benefit.

See Online Data Supplement D.

ESCAPE: Inpatient Mortality by Diuretic Dose

In 1785, Sir William Withering believed that digitalis purpurea had a diuretic effect in patients with a weak and irregular pulse who had edema.
Classification of Patients Presenting with Acutely Decompensated Heart Failure

<table>
<thead>
<tr>
<th>Low perfusion at rest? (e.g. narrow pulse pressure, cool extremities, hypotension)</th>
<th>Congestion at rest?</th>
<th>No</th>
<th>Yes</th>
</tr>
</thead>
<tbody>
<tr>
<td>No</td>
<td>Warm and Dry</td>
<td>Warm and Wet</td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>Cold and Dry</td>
<td>Cold and Wet</td>
<td></td>
</tr>
</tbody>
</table>
Physiologic Effects of RAAS: ACE Inhibition

- Chymase
- Renin
- Angiotensinogen
- Angiotensin I
- Angiotensin II
- ACE
- ACE-I
- AT1 Receptor
- AT2 Receptor
- Aldosterone
- Bradykinin/Kinins
- B1/B2-Receptor
- Degradation
- Nitric Oxide
- Vasoconstriction
- Reactive oxygen species
- Cellular growth
- Apoptosis
- Neurohumoral activation
- Vasodilation
- Growth inhibition
- Apoptosis
Schematic Representation of Mortality in Heart Failure Patients

CONSENSUS I (Class IV)¹
n=253
27% ↓ mortality
P=0.003

SOLVD-Treatment (Class II–III)³
n=2569
16% ↓ mortality
P=0.016

SOLVD-Prevention (Class I–II)⁴
n=4228
trend toward ↓ death

V-HeFT II (Class II–III)²
n=804
trend toward ↓ death

Renal Effects of Angiotensin II

Efferent > Afferent Arteriolar Constriction
(PRESSURE EFFECT)
Glomerular hypertension / hyperfiltration Proteinuria

Mesangial/Glomerular Constriction
(ENDOTHELIAL EFFECT)
↓ Glomerular Surface Area
↓ Filtration Constant $K_f$
Proteinuria
Production renal cytokines,
(eg TGF$_{BETA}$)
Proximal tubule Na reabsorption

Early Worsening Renal Function Status: Legend in lower right

Medical optimization and stabilization can take 3 months or more.

- Beta blocker doses effective in HF are generally achieved in 8 to 12 weeks and do not impart any mortality benefit until at least 3 months.

---

MERIT-HF: Clinical outcomes with β-blockade

<table>
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<tr>
<th>Risk reduction (%)</th>
<th>Sudden death</th>
<th>HF mortality</th>
<th>HF hospitalizations</th>
</tr>
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<tbody>
<tr>
<td></td>
<td>P = 0.0002</td>
<td>P = 0.0023</td>
<td></td>
</tr>
<tr>
<td></td>
<td>↓41</td>
<td>↓49</td>
<td>Number ↓30 (P &lt; 0.001)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Days in hospital ↓36 (P &lt; 0.001)</td>
</tr>
</tbody>
</table>

MERIT HF substudy: Effect of β-blockade on LV remodeling

- **LVEDV** = left ventricular end-diastolic volume
- **LVESV** = left ventricular end-systolic volume

Comparative Effects of Low and High Doses of the Angiotensin-Converting Enzyme Inhibitor, Lisinopril, on Morbidity and Mortality in Chronic Heart Failure

Figure 1. Kaplan-Meier analysis showing time to death in the low-dose and high-dose lisinopril groups. Solid line indicates low-dose group; dotted line, high-dose group. Compared with low-dose group, patients in high-dose group had an 8% lower risk, $P=0.128$.

# Optimizing Neurohormonal Therapy in HF Patients Receiving an ACE Inhibitor

<table>
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<th>Symptom/Action</th>
<th>Symptoms</th>
<th>Morbidity</th>
<th>Mortality</th>
</tr>
</thead>
<tbody>
<tr>
<td>Increase dose of ACE inhibitor$^1$</td>
<td>No effect</td>
<td>13%</td>
<td>NS</td>
</tr>
<tr>
<td>Add $\beta$-blocker$^2$</td>
<td>↓</td>
<td>↓ 37%</td>
<td>↓ 32%</td>
</tr>
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</table>

Medical Therapy for Stage C HFrEF: Magnitude of Benefit Demonstrated in RCTs

<table>
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<tr>
<th>GDMT</th>
<th>RR Reduction in Mortality (%)</th>
<th>NNT for Mortality Reduction (Standardized to 36 mo)</th>
<th>RR Reduction in HF Hospitalizations (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>ACE inhibitor or ARB</td>
<td>17</td>
<td>26</td>
<td>31</td>
</tr>
<tr>
<td>Beta blocker</td>
<td>34</td>
<td>9</td>
<td>41</td>
</tr>
<tr>
<td>Aldosterone antagonist</td>
<td>30</td>
<td>6</td>
<td>35</td>
</tr>
<tr>
<td>Hydralazine/nitrate</td>
<td>43</td>
<td>7</td>
<td>33</td>
</tr>
</tbody>
</table>

ACE indicates angiotensin-converting enzyme; ARB, angiotensin-receptor blocker; GDMT, guideline-directed medical therapy; HF, heart failure; HFrEF, heart failure with reduced ejection fraction; NNT, number needed to treat; RCTs, randomized controlled trials; and RR, relative risk.

Adapted with permission from Fonarow et al.\textsuperscript{201}

Cardiovascular Consequences of Aldosterone Excess

Aldosterone excess

- Cardiac fibrosis
- $K^+$ loss
- Mg$^{2+}$ loss
- Catechol potentiation
- ↓BR sensitivity
- Vascular fibrosis
- ↑Vascular reactivity
- Na$^+/H_2O$ retention

Arrhythmias

Hypertension

LVH

↓Diastolic and systolic function

Overt cardiac failure

Congestion

RALES: Aldosterone Receptor Blockade Improves Outcomes in Severe Heart Failure

RALES=Randomized Aldactone Evaluation Study

Rates of Hyperkalemia after Publication of the Randomized Aldactone Evaluation Study

Strategies to Minimize the Risk of Hyperkalemia in Patients Treated with Aldosterone Antagonists

1. Impaired renal function is a risk factor for hyperkalemia during treatment with aldosterone antagonists. The risk of hyperkalemia increases progressively when serum creatinine is $>1.6$ mg/dL.* In elderly patients or others with low muscle mass in whom serum creatinine does not accurately reflect glomerular filtration rate, determination that glomerular filtration rate or creatinine clearance is $>30$ mL/min/1.73 m$^2$ is recommended.

2. Aldosterone antagonists would not ordinarily be initiated in patients with baseline serum potassium $>5.0$ mEq/L.

3. An initial dose of spironolactone of 12.5 mg or eplerenone 25 mg is typical, after which the dose may be increased to spironolactone 25 mg or eplerenone 50 mg if appropriate.

4. The risk of hyperkalemia is increased with concomitant use of higher doses of ACE inhibitors (captopril $\geq 75$ mg daily; enalapril or lisinopril $\geq 10$ mg daily).

5. In most circumstances, potassium supplements are discontinued or reduced when initiating aldosterone antagonists.

6. Close monitoring of serum potassium is required; potassium levels and renal function are most typically checked in 3 d and at 1 wk after initiating therapy and at least monthly for the first 3 mo.

*Although the entry criteria for the trials of aldosterone antagonists included creatinine $<2.5$ mg/dL, the majority of patients had much lower creatinine; in 1 trial (425), 95% of patients had creatinine $\leq 1.7$ mg/dL.

ACE indicates angiotensin-converting enzyme.
Two-Year Mortality in Contemporary Clinical Trials (triple therapy)

Ivabradine and outcomes in chronic heart failure (SHIFT): a randomised placebo-controlled study

Karl Swedberg, Michel Komajda, Michael Böhm, Jeffrey S Borer, Ian Ford, Ariane Dubost-Brama, Guy Lerebours, Luigi Tavazzi, on behalf of the SHIFT Investigators*

Summary

Background Chronic heart failure is associated with high mortality and morbidity. Raised resting heart rate is a risk

28% reduction in HF hospitalizations

Angiotensin–Neprilysin Inhibition versus Enalapril in Heart Failure

John J.V. McMurray, M.D., Milton Packer, M.D., Akshay S. Desai, M.D., M.P.H., Jianjian Gong, Ph.D., Martin P. Lefkowitz, M.D., Adel R. Rizkala, Pharm.D., Jean L. Rouleau, M.D., Victor C. Shi, M.D., Scott D. Solomon, M.D., Karl Swedberg, M.D., Ph.D., and Michael R. Zile, M.D., for the PARADIGM-HF Investigators and Committees*

20% reduction in CV death, HF hospitalizations

Wireless pulmonary artery haemodynamic monitoring in chronic heart failure: a randomised controlled trial

William T Abraham, Philip B Adamson, Robert C Bourge, Mark F Aaron, Maria Rosa Costanzo, Lynne W Stevenson, Warren Strickland, Suresh Neelaguru, Nirav Raval, Steven Krueger, Stanislav Weiner, David Shavelle, Bradley Jeffries, Jay S Yadav, for the CHAMPION Trial Study Group*

Summary

Background Results of previous studies support the hypothesis that implantable haemodynamic monitoring systems might reduce rates of hospitalisation in patients with heart failure. We undertook a single-blind trial to assess this approach.

26% reduction in HF hospitalizations
Newly Approved Heart Failure Drug

Ivabradine

- Acts by inhibiting the If channel, present in the cardiac SA node
- Reduces persistently elevated heart rate
- Approved by FDA in April 2015 for stable HF pts who have a resting HR of at least 70 bpm, and who are also taking the highest tolerable dose of a beta blocker

### Baseline Characteristics of Patients in New Heart Failure Trials

<table>
<thead>
<tr>
<th></th>
<th></th>
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<th></th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>N</strong></td>
<td>6558</td>
<td>8442</td>
<td>550</td>
</tr>
<tr>
<td><strong>Tx</strong></td>
<td>Ivabradine</td>
<td>Entresto</td>
<td>Wireless PA sensor</td>
</tr>
<tr>
<td><strong>Inclusion Criteria</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>-HR &gt;70bpm</td>
<td></td>
<td>-NYHA II, III, IV</td>
<td>-NYHA III</td>
</tr>
<tr>
<td>-HF hosp. 12 months</td>
<td></td>
<td>-EF &lt;40%</td>
<td>-HF for 3 months</td>
</tr>
<tr>
<td>-EF &lt;35%</td>
<td></td>
<td>-BNP &gt;150 or NT-ProBNP &gt;600</td>
<td>-HF hosp. 12 mos</td>
</tr>
<tr>
<td>Exclusion Criteria</td>
<td></td>
<td>SBP &lt;100mmHg</td>
<td>Stage III kidney disease</td>
</tr>
<tr>
<td>Age (years)</td>
<td>60.7</td>
<td>63.8</td>
<td>61</td>
</tr>
<tr>
<td>HR (BPM)</td>
<td>79</td>
<td>72</td>
<td>72</td>
</tr>
<tr>
<td>SBP (mmHg)</td>
<td>122</td>
<td>122</td>
<td>121</td>
</tr>
<tr>
<td>EF (%)</td>
<td>29</td>
<td>29.6</td>
<td>740, 23</td>
</tr>
<tr>
<td>Class II (%)</td>
<td>49</td>
<td>71</td>
<td>---</td>
</tr>
<tr>
<td>III (%)</td>
<td>50</td>
<td>23</td>
<td>100</td>
</tr>
<tr>
<td>IV (%)</td>
<td>2</td>
<td>0.8</td>
<td>---</td>
</tr>
<tr>
<td>BB (%)</td>
<td>89</td>
<td>93</td>
<td>90</td>
</tr>
<tr>
<td>AA (%)</td>
<td>84</td>
<td>54</td>
<td>76</td>
</tr>
<tr>
<td>CV Mortality Benefit</td>
<td>No</td>
<td>Yes (21% reduction)</td>
<td>No</td>
</tr>
<tr>
<td>HF Readmission Benefit</td>
<td>Yes (26% reduction)</td>
<td>Yes (21% reduction)</td>
<td>Yes (28% reduction)</td>
</tr>
</tbody>
</table>
Mean Heart Rate During the Study in the Total Study Population, by Allocation Groups

Effect of Treatment on Primary Composite Endpoint of CV Death or Hospital Admission for Worsening HF in Prespecified Subgroups

<table>
<thead>
<tr>
<th>Subgroup</th>
<th>Ivabradine group</th>
<th>Placebo group</th>
<th>HR (95% CI)</th>
<th>Test for interaction</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Age</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;65 years (n=4031)</td>
<td>407 (20.5%)</td>
<td>527 (25.6%)</td>
<td>0.76 (0.67-0.87)</td>
<td>p=0.099</td>
</tr>
<tr>
<td>≥65 years (n=2474)</td>
<td>386 (30.5%)</td>
<td>410 (33.9%)</td>
<td>0.89 (0.77-1.02)</td>
<td></td>
</tr>
<tr>
<td><strong>Sex</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male (n=4970)</td>
<td>624 (25.4%)</td>
<td>725 (28.9%)</td>
<td>0.84 (0.76-0.94)</td>
<td>p=0.260</td>
</tr>
<tr>
<td>Female (n=1535)</td>
<td>169 (21.7%)</td>
<td>212 (28.0%)</td>
<td>0.74 (0.60-0.91)</td>
<td></td>
</tr>
<tr>
<td><strong>β-blockers</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No β-blocker intake at randomisation (n=685)</td>
<td>101 (29.4%)</td>
<td>134 (39.3%)</td>
<td>0.68 (0.52-0.88)</td>
<td>p=0.103</td>
</tr>
<tr>
<td>β-blocker intake at randomisation (n=5820)</td>
<td>692 (23.9%)</td>
<td>803 (27.5%)</td>
<td>0.85 (0.76-0.94)</td>
<td></td>
</tr>
<tr>
<td><strong>Cause of heart failure</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Non-ischaemic (n=2087)</td>
<td>218 (21.3%)</td>
<td>296 (27.9%)</td>
<td>0.72 (0.60-0.85)</td>
<td>p=0.059</td>
</tr>
<tr>
<td>Ischaemic (n=4418)</td>
<td>575 (26.0%)</td>
<td>641 (29.1%)</td>
<td>0.87 (0.78-0.97)</td>
<td></td>
</tr>
<tr>
<td><strong>NYHA class</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>NYHA class II (n=3169)</td>
<td>300 (18.9%)</td>
<td>356 (22.5%)</td>
<td>0.81 (0.69-0.94)</td>
<td>p=0.793</td>
</tr>
<tr>
<td>NYHA class III or IV (n=3334)</td>
<td>493 (29.8%)</td>
<td>580 (34.5%)</td>
<td>0.83 (0.74-0.94)</td>
<td></td>
</tr>
<tr>
<td><strong>Diabetes</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No history of diabetes (n=4526)</td>
<td>525 (23.2%)</td>
<td>611 (27.1%)</td>
<td>0.83 (0.74-0.93)</td>
<td>p=0.861</td>
</tr>
<tr>
<td>History of diabetes (n=1979)</td>
<td>268 (27.5%)</td>
<td>326 (32.4%)</td>
<td>0.81 (0.69-0.95)</td>
<td></td>
</tr>
<tr>
<td><strong>Hypertension</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No history of hypertension (n=2191)</td>
<td>274 (25.4%)</td>
<td>330 (29.7%)</td>
<td>0.81 (0.69-0.95)</td>
<td>p=0.779</td>
</tr>
<tr>
<td>History of hypertension (n=4314)</td>
<td>519 (24.0%)</td>
<td>607 (28.2%)</td>
<td>0.83 (0.74-0.93)</td>
<td></td>
</tr>
<tr>
<td><strong>Baseline heart rate</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;77 bpm (n=3144)</td>
<td>339 (21.4%)</td>
<td>356 (22.8%)</td>
<td>0.93 (0.80-1.08)</td>
<td>p=0.029</td>
</tr>
<tr>
<td>≥77 bpm (n=3357)</td>
<td>454 (27.4%)</td>
<td>581 (34.2%)</td>
<td>0.75 (0.67-0.85)</td>
<td></td>
</tr>
</tbody>
</table>

## Recommendations for Ivabradine

<table>
<thead>
<tr>
<th>COR</th>
<th>LOE</th>
<th>Recommendation</th>
<th>Comment/Rationale</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 HFpEF (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 (154-157).</td>
<td>NEW: New clinical trial data.</td>
</tr>
</tbody>
</table>

Ivabradine is a new therapeutic agent that selectively inhibits the If 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 (155). The benefit of ivabradine was driven by a reduction in HF hospitalization. The study included patients with HFpEF (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

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Angiotensin–Neprilysin Inhibition versus Enalapril in Heart Failure

John J.V. McMurray, M.D., Milton Packer, M.D., Akshay S. Desai, M.D., M.P.H., Jianjian Gong, Ph.D., Martin P. Lefkowitz, M.D., Adel R. Rizkala, Pharm.D., Jean L. Rouleau, M.D., Victor C. Shi, M.D., Scott D. Solomon, M.D., Karl Swedberg, M.D., Ph.D., and Michael R. Zile, M.D., for the PARADIGM-HF Investigators and Committees*
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PARADIGM-HF
(Prospective Comparison of ARNI with ACEI to Determine Impact on Global Mortality and Morbidity in Heart Failure trial)

HR: 0.80 (0.73, 0.87) p = 0.0000004

Death from CV causes 20% risk reduction

HF hospitalization 21% risk reduction
Sacubitril and Valsartan (Entresto)

Natriuretic peptide system

pro-BNP → BNP → NT-pro-BNP

Vasodilation:
- Blood pressure
- Sympathetic tone
- Aldosterone levels
- Fibrosis
- Hypertrophy
- Natriuresis
- Diuresis

inactive fragments → Neprilysin → Angiotensin II

Vasoconstriction:
- Blood pressure
- Sympathetic tone
- Aldosterone levels
- Fibrosis
- Hypertrophy
- Sodium retention
- Water retention

Abbreviations: AT1, angiotensin 1; BNP, brain natriuretic peptides.

Based on Figure 1, Swedberg Nature Reviews Cardiology 2015.
Figure 1 Kaplan–Meier survival curve for sudden death, by treatment. HR, hazard ratio.
Pearls on Neprilysin Inhibition

- Cannot measure BNP for management of heart failure
- Cannot be administered concomitantly with ACE inhibitor or within 36 hours of last dose of ACE inhibitor.
- Risk of hypotension, renal insufficiency, angioedema
- Consider in ACE failure HF patient
  - Hospitalization for HF
  - Symptomatic HF Class II, III
  - Elevated BNP (150), NT-ProBNP (600)
  - On maximum optimize BB dose
  - SBP >100 mmHg (warm, wet)
  - New onset HF?
## Prespecified Subgroup Analysis Paradigm HF

<table>
<thead>
<tr>
<th>Condition</th>
<th>No</th>
<th>552/2,670 (20.7)</th>
<th>637/2,638 (24.1)</th>
<th>36.2</th>
<th>362/1,517 (23.9)</th>
<th>480/1,574 (30.5)</th>
<th>63.2</th>
</tr>
</thead>
<tbody>
<tr>
<td>Atrial fibrillation</td>
<td>Yes</td>
<td>299/2,079 (14.4)</td>
<td>403/2,116 (19.0)</td>
<td>49.9</td>
<td>614/2,103 (29.2)</td>
<td>711/2,087 (34.1)</td>
<td>49.9</td>
</tr>
<tr>
<td>NT-proBNP</td>
<td>≤Median</td>
<td>245/1,218 (20.1)</td>
<td>303/1,241 (24.4)</td>
<td>29.3</td>
<td>669/2,969 (22.5)</td>
<td>814/2,971 (27.4)</td>
<td>70.7</td>
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<tr>
<td>Hypertension</td>
<td>Yes</td>
<td>691/3,258 (21.2)</td>
<td>866/3,249 (26.7)</td>
<td>77.5</td>
<td>223/929 (24.0)</td>
<td>251/963 (26.1)</td>
<td>22.5</td>
</tr>
<tr>
<td>Prior use of ACE inhibitor</td>
<td>No</td>
<td>399/1,916 (20.8)</td>
<td>494/1,812 (27.3)</td>
<td>44.4</td>
<td>515/2,271 (22.7)</td>
<td>623/2,400 (26.0)</td>
<td>55.6</td>
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<tr>
<td>Prior use of ARB</td>
<td>Yes</td>
<td>262/1,580 (16.6)</td>
<td>348/1,545 (22.5)</td>
<td>77.2</td>
<td>652/2,607 (25.0)</td>
<td>769/2,667 (28.8)</td>
<td>62.8</td>
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<tr>
<td>Prior hospitalization for heart failure</td>
<td>No</td>
<td>202/1,275 (15.8)</td>
<td>240/1,248 (19.2)</td>
<td>30.0</td>
<td>392/1,621 (24.2)</td>
<td>447/1,611 (27.7)</td>
<td>38.5</td>
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<tr>
<td>Time since diagnosis of heart failure</td>
<td>Yes</td>
<td>320/1,291 (24.8)</td>
<td>430/1,353 (31.8)</td>
<td>31.5</td>
<td>339/1,681 (20.2)</td>
<td>420/1,682 (25.0)</td>
<td>40.0</td>
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<tr>
<td>Cause of heart failure</td>
<td>Non-ischemic</td>
<td>575/2,506 (22.9)</td>
<td>697/2,530 (27.5)</td>
<td>60.0</td>
<td>761/3,564 (21.4)</td>
<td>942/3,592 (26.2)</td>
<td>85.2</td>
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<tr>
<td>Any ICD (including CRT-D)</td>
<td>No</td>
<td>153/623 (24.6)</td>
<td>175/620 (28.2)</td>
<td>14.8</td>
<td>362/1,517 (23.9)</td>
<td>480/1,574 (30.5)</td>
<td>63.2</td>
</tr>
</tbody>
</table>
Study Design Paradigm HF

**Single-blind Active Run-in Period**
- Enalapril run-in
  - Visit 2A
  - Enalapril 5 mg bid (optional)
  - 1-2w

**Double-blind Treatment Period**
- LCZ696 run-in
- LCZ696 200 mg bid
- Enalapril 10 mg bid

**Time**
- Visit 1
  - 1w
- Visit 2
  - 2w
- Visit 3
  - 1-2w
- Visit 4
  - 2-4w
- Visit 5
  - 0
- Visit 6
  - 2w
- Visit 7
  - 4w
- Visit 8
  - 8w
- Visit 9
  - 4m
- Visit 10
  - 8m
- Visit every 4m until end of study
Therapeutic Algorithm for a Patient with Symptomatic Heart Failure with Reduced Ejection Fraction

Treatment Algorithm for GDMT Including Novel Therapies

HFrEF

ACE/ARB and BB with Diuretic as Needed

For patients with persistent volume overload, NYHA class II-IV
- Titrate
  - Diuretics (Figure 3C)

For persistently symptomatic African Americans, NYHA class III-IV
- Add
  - Hydralazine + isosorbide dinitrate (Figure 3D)

For patients stable on ACEI/ARB, NYHA class II-III
- Switch
  - ARNI (Figure 3E)

For patients with eGFR ≥ 30mL/min/1.72 m², K⁺ < 5.0 mEq/dL, NYHA class II-IV
- Add
  - Aldosterone Antagonist (Figure 3F)

For patients with resting HR ≥ 70, on maximally tolerated beta blocker dose in sinus rhythm, NYHA class II-III
- Add
  - Ivabradine (Figure 3G)

Angiotensin–Neprilysin Inhibition in Acute Decompensated Heart Failure

Eric J. Velazquez, M.D., David A. Morrow, M.D., M.P.H., Adam D. DeVore, M.D., M.H.S., Carol I. Duffy, D.O., Andrew P. Ambrosy, M.D., Kevin McCague, M.A., Ricardo Rocha, M.D., and Eugene Braunwald, M.D., for the PIONEER-HF Investigators*

Change in NT-proBNP Concentration (N=881)

Change in NT-proBNP from Baseline (%)

![Graph showing change in NT-proBNP concentration over weeks since randomization]

No. at Risk

<table>
<thead>
<tr>
<th></th>
<th>Baseline</th>
<th>1</th>
<th>2</th>
<th>3</th>
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<th>5</th>
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<tr>
<td>Enalapril</td>
<td>394</td>
<td>359</td>
<td>351</td>
<td>350</td>
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<tr>
<td>Sacubitril–valsartan</td>
<td>397</td>
<td>355</td>
<td>363</td>
<td>365</td>
<td>365</td>
<td>349</td>
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Los Tres Grandes: ARNI, Beta Blocker, Aldo antagonist