Sacubitril/Valsartan: Why, Who, When, How?

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Neprilysin as a Therapeutic Target

- Neprilysin is responsible for the breakdown of a number of endogenous vasoactive peptides, including the natriuretic peptides.

- Inhibition of neprilysin potentiates the action of those peptides.

- Because angiotensin II is also a substrate for neprilysin, neprilysin inhibitors must be co-administered with a RAAS blocker.

- The combination of a neprilysin inhibitor and an ACE-inhibitor is associated with unacceptably high rates of angioedema.

Natriuretic Peptides
- Adrenomedullin
- Bradykinin
- Substance P (angiotensin II)

Neprilysin

Inactive fragments
Sacubitril/Valsartan (LCZ696): A first-in-class angiotensin/neprilysin inhibitor (ARNi)

LCZ696 is a novel crystalline complex consisting of the molecular moieties of valsartan and sacubitril in an equimolar ratio.

Sacubitril \( \downarrow \) LBQ657

Neprilysin Inhibitor

+ ARB

Dissociates at low pH
## PARADIGM-HF: Entry Criteria

<table>
<thead>
<tr>
<th>Key Inclusion Criteria</th>
<th>Key Exclusion Criteria</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Chronic HF NYHA class II–IV with LVEF ≤40% (which was amended to ≤35% one year after study started) and:</td>
<td>• History of angioedema</td>
</tr>
<tr>
<td>– BNP ≥150 pg/mL (or NT-proBNP ≥ 600) OR</td>
<td>• eGFR &lt;30 mL/min/1.73 m²</td>
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<tr>
<td>– BNP ≥100 pg/mL (or NT-proBNP ≥ 400) + HF hospitalization last 12 months</td>
<td>• Serum potassium &gt;5.2 mmol/L</td>
</tr>
<tr>
<td>• Stable on ACEI or ARB (dosage equivalent to enalapril ≥10 mg/d) for 4 weeks</td>
<td>• Symptomatic hypotension, SBP &lt;100 mmHg</td>
</tr>
<tr>
<td>• β-blocker for 4 weeks, unless not tolerated</td>
<td>• Current acute decompensated HF</td>
</tr>
<tr>
<td>• Optimized dosing of background HF medications (MRA)</td>
<td></td>
</tr>
</tbody>
</table>
PARADIGM-HF Study Design

Randomization

Single-blind run-in period (N=10,521)
- 2 weeks
- 1-2 weeks
- 2-4 weeks
19.7% Attrition

Enalapril
- 10 mg BID
- 100 mg BID
- 200 mg BID

LCZ696
- 100 mg BID
- 200 mg BID

Double-blind period (N=8399)
(1:1 randomization)

Sacubitril/Valsartan 97/103 mg BID

Median Follow up 27 Months

Enalapril 10 mg BID
Predictors of Run-in Noncompletion

- Lower eGFR
- Higher NT-proBNP
- Lower Systolic BP
- Ischemic cause of heart Failure

Those who dropped out share many characteristics with those who were randomized.

Overweighting patients similar to those who dropped out does not alter study results.

Desai et al. Circulation 2016
<table>
<thead>
<tr>
<th></th>
<th><strong>LCZ696 (n=4187)</strong></th>
<th><strong>Enalapril (n=4212)</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>63.8 ± 11.5</td>
<td>63.8 ± 11.3</td>
</tr>
<tr>
<td>Women (%)</td>
<td>21.0%</td>
<td>22.6%</td>
</tr>
<tr>
<td>Ischemic cardiomyopathy (%)</td>
<td>59.9%</td>
<td>60.1%</td>
</tr>
<tr>
<td>LV ejection fraction (%)</td>
<td>29.6 ± 6.1</td>
<td>29.4 ± 6.3</td>
</tr>
<tr>
<td>NYHA functional class II / III (%)</td>
<td>71.6% / 23.1%</td>
<td>69.4% / 24.9%</td>
</tr>
<tr>
<td>Systolic blood pressure (mm Hg)</td>
<td>122 ± 15</td>
<td>121 ± 15</td>
</tr>
<tr>
<td>Heart rate (beats/min)</td>
<td>72 ± 12</td>
<td>73 ± 12</td>
</tr>
<tr>
<td>N-terminal pro-BNP (pg/ml)</td>
<td>1631 (885-3154)</td>
<td>1594 (886-3305)</td>
</tr>
<tr>
<td>B-type natriuretic peptide (pg/ml)</td>
<td>255 (155-474)</td>
<td>251 (153-465)</td>
</tr>
<tr>
<td>History of diabetes</td>
<td>35%</td>
<td>35%</td>
</tr>
<tr>
<td>Digitalis</td>
<td>29.3%</td>
<td>31.2%</td>
</tr>
<tr>
<td>Beta-adrenergic blockers</td>
<td>93.1%</td>
<td>92.9%</td>
</tr>
<tr>
<td>Mineralocorticoid antagonists</td>
<td>54.2%</td>
<td>57.0%</td>
</tr>
<tr>
<td>ICD and/or CRT</td>
<td>16.5%</td>
<td>16.3%</td>
</tr>
</tbody>
</table>
PARADIGM-HF: CV Death or HF Hospitalization (Primary Endpoint)

Kaplan-Meier Estimate of Cumulative Rates (%)

- Enalapril (n=4212)
  - Kaplan-Meier Estimate of Cumulative Rates (%)
  - 15% at 1 yr

- LCZ696 (n=4187)
  - Kaplan-Meier Estimate of Cumulative Rates (%)
  - HR = 0.80 (0.73-0.87)
  - P = 0.0000004
  - Number needed to treat = 21

Patients at Risk
- LCZ696: 4187
- Enalapril: 4212

Days After Randomization

McMurray et al. NEJM 2014
Other Key Endpoints

- Cardiovascular death: ↓20% (16.5% vs. 13.3%)
- HF hospitalization: ↓20% (15.6% vs. 12.8%)
- Overall mortality: ↓16% (19.8% vs. 17.0%)
- HF death: ↓21% (4.4% vs. 3.5%)
- Sudden death: ↓20% (7.4% vs. 6.0%)

McMurray, NEJM 2014; Desai et al. European Heart Journal 2015
Doubling of Survival over ACE/ARB

Estimated 1-2 year increase in life expectancy with LCZ696 over enalapril

McMurray et al. EHJ 2015; Claggett, et al NEJM 2015
Consistent Benefits Across a Spectrum of HF Severity

CV death or HF hospitalisation

- **Enalapril**
- **LCZ696**

Increasing risk of CV death/HF hospitalization

Simpson J, et al. JACC 2015
Heart Failure Progression

Time to First HF Hospitalization (first 30 days)

Cumulative HF Hospitalizations

Fewer LCZ696-treated patients experienced worsening HF symptoms or required intensification of medical treatment, emergency department evaluation, intensive care, or inotropic support for HF.

Impact on Readmissions

- 30-day All-cause Readmission:
  - Enalapril: 21.0%
  - LCZ696: 17.8%

- 30-day Heart Failure Readmission:
  - Enalapril: 13.4%
  - LCZ696: 9.7%

- 60-day All-cause Readmission:
  - Enalapril: 30.5%
  - LCZ696: 27.8%

- 60-day Heart Failure Readmission:
  - Enalapril: 20.3%
  - LCZ696: 17.1%

## PARADIGM-HF: Safety

<table>
<thead>
<tr>
<th>Prospectively identified adverse events</th>
<th>LCZ696 (n=4187)</th>
<th>Enalapril (n=4212)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Symptomatic hypotension</td>
<td>588 (14%)</td>
<td>388 (9.2%)</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Serum potassium &gt; 6.0 mmol/l</td>
<td>181 (4.3%)</td>
<td>236 (5.6%)</td>
<td>0.007</td>
</tr>
<tr>
<td>Serum creatinine ≥ 2.5 mg/dl</td>
<td>139 (3.3%)</td>
<td>188 (4.5%)</td>
<td>0.007</td>
</tr>
<tr>
<td>Cough</td>
<td>474 (11.3%)</td>
<td>601 (14.3%)</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Discontinuation for adverse event</td>
<td>449</td>
<td>516</td>
<td>0.02</td>
</tr>
<tr>
<td>Discontinuation for hypotension</td>
<td>36</td>
<td>29</td>
<td>NS</td>
</tr>
<tr>
<td>Discontinuation for hyperkalemia</td>
<td>11</td>
<td>15</td>
<td>NS</td>
</tr>
<tr>
<td>Discontinuation for renal impairment</td>
<td>29</td>
<td>59</td>
<td>0.001</td>
</tr>
<tr>
<td>Angioedema (adjudicated)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Medications, no hospitalization</td>
<td>16 (0.3%)</td>
<td>9 (0.2%)</td>
<td>NS</td>
</tr>
<tr>
<td>Hospitalized; no airway compromise</td>
<td>3 (0.1%)</td>
<td>1 (&lt;0.1%)</td>
<td>NS</td>
</tr>
<tr>
<td>Airway compromise</td>
<td>0</td>
<td>0</td>
<td>----</td>
</tr>
</tbody>
</table>
## Guideline Update

**2016 ACC/AHA/HFSA Focused Update on New Pharmacological Therapy for Heart Failure: An Update of the 2013 ACCF/AHA Guideline for the Management of Heart Failure**

<table>
<thead>
<tr>
<th>COR</th>
<th>LOE</th>
<th>Recommendations</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>B-R</td>
<td>ACEi OR ARB OR ARNI in conjunction with beta-blockers + MRA (where appropriate) is recommended for patients with chronic HFrEF to reduce morbidity and mortality.</td>
</tr>
<tr>
<td>I</td>
<td>B-R</td>
<td>In patients with chronic, symptomatic HFrEF NYHA class II or III who tolerate and ACE inhibitor or ARB, replacement by an ARNI is recommended to further reduce morbidity and mortality</td>
</tr>
<tr>
<td>III</td>
<td>B-R</td>
<td>ARNI should NOT be administered concomitantly with ACEi or within 36 hours of last ACEi dose</td>
</tr>
<tr>
<td>III</td>
<td>C=EO</td>
<td>ARNI should NOT be administered to patients with a history of angioedema</td>
</tr>
</tbody>
</table>

A New Paradigm?

Optimize ‘standard regimen’ first?

Timing of introduction of spironolactone?

Different approach in African Americans?
How to Initiate?

- Initiation
  - 36 hour gap between discontinuation of ACE and initiation of sacubitril/valsartan

- Dosing

<table>
<thead>
<tr>
<th>Population</th>
<th>Initial Dose</th>
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<tbody>
<tr>
<td>Routine</td>
<td>49/51 mg twice daily</td>
</tr>
<tr>
<td>Low dose ACE/ARB</td>
<td></td>
</tr>
<tr>
<td>ACE/ARB naïve</td>
<td></td>
</tr>
<tr>
<td>eGFR&lt;=30 mL/min/m²</td>
<td>24/26 mg twice daily</td>
</tr>
<tr>
<td>Moderate Hepatic Impairment (Child-Pugh Class B)</td>
<td></td>
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<tr>
<td>Elderly</td>
<td></td>
</tr>
</tbody>
</table>

- Titration
  - Double dose every 2-4 weeks until target dose of 97/103 mg twice daily is reached
Summary:
Selecting Patients for Sacubitril/Valsartan

• Yes
  – NYHA II-III subjects tolerating ACE/ARB

• Maybe
  – Subjects on low dose ACE/ARB
  – ACE/ARB naïve subjects

• No Data
  – Stage D HF
  – Hospitalized HF patients
  – HF with Preserved EF
Thank You!