Efficacy and Safety of Sacubitril/Valsartan in High-Risk Patients in the PIONEER-HF Trial

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Disclosures

• I have no personal disclosures

• The PIONEER-HF trial was sponsored by Novartis
Background

- Pts with ADHF are at high risk for poor outcomes, including complications of therapy
- Among pts with HFrEF hospitalized for ADHF, in-hospital initiation of sacubitril/valsartan vs. enalapril was well-tolerated and led to a greater ↓ in NT-proBNP and ↓ rHHF/CVD

**Change in NT-proBNP**

<table>
<thead>
<tr>
<th>Weeks from Randomization</th>
<th>Change in NT-proBNP from Baseline (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baseline</td>
<td>Sacubitril/Valsartan</td>
</tr>
<tr>
<td>1</td>
<td>-60</td>
</tr>
<tr>
<td>2</td>
<td>-50</td>
</tr>
<tr>
<td>3</td>
<td>-40</td>
</tr>
<tr>
<td>4</td>
<td>-30</td>
</tr>
<tr>
<td>5</td>
<td>-20</td>
</tr>
<tr>
<td>6</td>
<td>-10</td>
</tr>
<tr>
<td>7</td>
<td>0</td>
</tr>
<tr>
<td>8</td>
<td>10</td>
</tr>
</tbody>
</table>

**Re-Hospitalization for HF or CV Death**

<table>
<thead>
<tr>
<th>Weeks from Randomization</th>
<th>Percent of Patients with CVD/HF</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>Enalapril</td>
</tr>
<tr>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>2</td>
<td>5</td>
</tr>
<tr>
<td>3</td>
<td>10</td>
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<tr>
<td>4</td>
<td>15</td>
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<tr>
<td>5</td>
<td>20</td>
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<tr>
<td>6</td>
<td>25</td>
</tr>
<tr>
<td>7</td>
<td>30</td>
</tr>
<tr>
<td>8</td>
<td>35</td>
</tr>
</tbody>
</table>


Objective

Given heightened clinical concern about in-hospital initiation of sacubitril/valsartan in *pts at higher risk of complications*, we assessed outcomes in *selected high-risk subgroups* in PIONEER-HF.
Study Design

*N = 881*

Hospitalized with ADHF (EF≤40%)

**Sacubitril/valsartan**
Target: 97/103 mg twice daily

**Enalapril**
Target: 10 mg twice daily

In-hospital initiation

Evaluate
- NTproBNP
- Safety and tolerability
- Clinical outcomes

**Stabilized while still hospitalized**
- SBP ≥100 mmHg in prior 6h; no symptomatic ↓ BP
- No increase in IV diuretics in prior 6h
- No IV vasodilators in prior 6h
- No IV inotropes in prior 24h

Blinded Study Rx for 8 weeks

Velazquez et al. AHJ 2018;198:145-51
High-Risk Subgroups

- SBP ≤118 mmHg (median) (n=440)
- LVEF ≤25% (n=573)
- NYHA class III/IV (n=627)
- NT-proBNP concentration >2701 pg/ml (median) (n=440)
- eGFR <60 ml/min/1.73 m² (n=455)
- ≥1 additional HHF within the prior year (n=343)
- Admission to the ICU during the index hospitalization (n=96)
- Use of inotropes during the index hospitalization (n=68)
Rehospitalization for HF or CV Death (8 Weeks)

Overall RR (Sacubitril/Valsartan vs. Enalapril) 0.58 (95% CI, 0.39-0.87)

- **SBP at randomization**
  - P-interaction = 0.67
  - ≤118 mmHg: 17.2% (Enalapril), 11.0% (Sacubitril/Valsartan)
  - >118 mmHg: 13.2% (Enalapril), 7.3% (Sacubitril/Valsartan)

- **LVEF at screening**
  - P-interaction = 0.59
  - ≤25%: 15.6% (Enalapril), 8.6% (Sacubitril/Valsartan)
  - >25%: 14.5% (Enalapril), 10.3% (Sacubitril/Valsartan)

- **NYHA class at randomization**
  - P-interaction = 0.96
  - Class III/IV: 16.2% (Enalapril), 9.3% (Sacubitril/Valsartan)
  - Class I/II: 12.7% (Enalapril), 6.9% (Sacubitril/Valsartan)

- **NT-proBNP at randomization**
  - P-interaction = 0.27
  - >2701 pg/ml: 16.3% (Enalapril), 12.1% (Sacubitril/Valsartan)
  - ≤2701 pg/ml: 10.2% (Enalapril), 4.3% (Sacubitril/Valsartan)

- **eGFR at randomization**
  - P-interaction = 0.29
  - <60: 15.5% (Enalapril), 11.4% (Sacubitril/Valsartan)
  - ≥60: 13.5% (Enalapril), 6.3% (Sacubitril/Valsartan)

- **HF hospitalization in past year**
  - P-interaction = 0.46
  - Yes: 19.9% (Enalapril), 13.4% (Sacubitril/Valsartan)
  - No: 12.5% (Enalapril), 6.3% (Sacubitril/Valsartan)

- **ICU admission for ADHF**
  - P-interaction = 0.22
  - Yes: 26.5% (Enalapril), 9.1% (Sacubitril/Valsartan)
  - No: 13.8% (Enalapril), 9.2% (Sacubitril/Valsartan)

- **On inotropes during admission**
  - P-interaction = 0.85
  - Yes: 20.1% (Enalapril), 13.2% (Sacubitril/Valsartan)
  - No: 14.8% (Enalapril), 8.8% (Sacubitril/Valsartan)

- **Rehospitalization for HF or CV Death (8 Weeks)**
  - Enalapril: 17.2%
  - Sacubitril/Valsartan: 11.0%

- **Overall RR (Sacubitril/Valsartan vs. Enalapril)**
  - 0.58 (95% CI, 0.39-0.87)
Worsening Renal Function through 8 Weeks

Overall RR (Sacubitril/Valsartan vs. Enalapril) 0.93 (95% CI, 0.67-1.28)

- **Baseline eGFR (ml/min/1.73 m²)**
  - Enalapril
  - Sacubitril/valsartan

  - **P-interaction = 0.32**

- **NT-proBNP at Randomization (pg/ml)**
  - NT-proBNP >2701
  - NT-proBNP ≤2701

  - **P-interaction = 0.41**

- **ICU Admission During Index Hospitalization**
  - Yes
  - No

  - **P-interaction = 0.57**

0 5 10 15 20 25 30 35

Worsening Renal Fxn at 8 weeks (%)

Enalapril
Sacubitril/valsartan

ScientificSessions.org #AHA19
Symptomatic Hypotension through 8 Weeks

Overall RR (Sacubitril/Valsartan vs. Enalapril) 1.18 (95% CI, 0.85-1.64)

- SBP at Randomization (mmHg)
  - SBP ≤118 mmHg: 15.3%, 17.8%
  - SBP >118 mmHg: 10.1%, 12.2%
  - P-interaction = 0.93

- Use of Inotropes During Index Hospitalization
  - Inotropes: 27.8%, 18.8%
  - No Inotropes: 11.4%, 14.7%
  - P-interaction = 0.19

SBP at Randomization (mmHg)

Use of Inotropes During Index Hospitalization
Summary

• In HFrEF patients hospitalized with ADHF at potentially higher risk of complications, there was a robust treatment effect and no evidence of lack of tolerability of sacubitril/valsartan vs. enalapril.

• Consistent with the overall trial result, these data support in-hospital initiation of sacubitril/valsartan in even the most vulnerable patients with HFrEF who are stabilized during hospitalization for ADHF.
Thank you!