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


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

**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

**In-hospital initiation**

- **Evaluated**
  - NTproBNP
  - Safety and tolerability
  - Clinical outcomes

- **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
  - 17.2% ≤118 mmHg
  - 11.0% >118 mmHg
  - 7.3%

- **LVEF at screening**
  - P-interaction = 0.59
  - 15.6% ≤25%
  - 14.5% >25%
  - 10.3%

- **NYHA class at randomization**
  - P-interaction = 0.96
  - 16.2% Class III/IV
  - 9.3% Class I/II
  - 12.7%

- **NT-proBNP at randomization**
  - P-interaction = 0.27
  - 16.3% >2701 pg/ml
  - 12.1% ≤2701 pg/ml
  - 10.2%

- **eGFR at randomization**
  - P-interaction = 0.29
  - 15.5% <60
  - 11.4% ≥60
  - 6.3%

- **HF hospitalization in past year**
  - P-interaction = 0.46
  - 19.9% Yes
  - 13.4% No
  - 12.5%

- **ICU admission for ADHF**
  - P-interaction = 0.22
  - 26.5% Yes
  - 9.1% No
  - 13.8%

- **On inotropes during admission**
  - P-interaction = 0.85
  - 20.1% Yes
  - 13.2% No
  - 14.8%

**Enalapril**

**Sacubitril/valsartan**
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)**

- **P-interaction = 0.32**
  - eGFR <60: 18.9% (Enalapril) vs. 15.4% (Sacubitril/Valsartan)
  - eGFR ≥60: 11.2% (Enalapril) vs. 12.8% (Sacubitril/Valsartan)

**NT-proBNP at Randomization (pg/ml)**

- **P-interaction = 0.41**
  - NT-proBNP >2701: 18.3% (Enalapril) vs. 13.9% (Sacubitril/Valsartan)
  - NT-proBNP ≤2701: 18.7% (Enalapril) vs. 10.6% (Sacubitril/Valsartan)

**ICU Admission During Index Hospitalization**

- **P-interaction = 0.57**
  - Yes: 23.5% (Enalapril) vs. 13.6% (Sacubitril/Valsartan)
  - No: 17.8% (Enalapril) vs. 13.2% (Sacubitril/Valsartan)
Symptomatic Hypotension through 8 Weeks

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

<table>
<thead>
<tr>
<th>SBP at Randomization (mmHg)</th>
<th>Symptomatic Hypotension at 8 weeks (%)</th>
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<tr>
<td>SBP ≤118 mmHg</td>
<td>Enalapril: 15.3% Sacubitril/Valsartan: 17.8%</td>
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<td><em>P</em>-interaction = 0.93</td>
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<td>SBP &gt;118 mmHg</td>
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Overall RR (Sacubitril/Valsartan vs. Enalapril) 1.18 (95% CI, 0.85-1.64)

SBP at Randomization (mmHg)

*P*-interaction = 0.93

Use of Inotropes During Index Hospitalization

*P*-interaction = 0.19
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!