Angiotensin Receptor-Neprilysin Inhibition in Patients Hospitalized With Acute Decompensated Heart Failure

Eric J Velazquez,1 David A Morrow,2 Adam D DeVore,3 Carol I Duffy,4 Andrew P Ambrosy,3 Kevin McCague,4 Ricardo Rocha,4 Eugene Braunwald2

1Yale Univ Sch of Med, New Haven, CT; 2Harvard Univ/Brigham and Women's Hosp, Boston, MA; 3Duke Univ/Duke Clinical Res Inst, Durham, NC; 4Novartis Pharmaceuticals Corp, East Hanover, NJ; 5
Background

- Acute decompensated heart failure (ADHF) accounts for over 1M hospitalizations in the US annually.
- Guideline-directed therapy for ADHF is limited.
  - Decongestion with diuretics and hemodynamic support with vasodilators remain the standards of care.
Rationale

- PARADIGM-HF trial in chronic HFrEF: sacubitril/valsartan ➔ CV death or HF hospitalization compared to enalapril
  - Patients with ADHF requiring IV therapy were excluded
  - Stable HF therapy with adequate doses for >4 weeks
  - Required sequential run-in with high dose enalapril and sacubitril/valsartan before randomization

- It is unknown if in-hospital initiation of sacubitril/valsartan compared to enalapril is safe and effective in ADHF

Study Design

Hospitalized with ADHF (HFrEF) → Stabilized → sacubitril/valsartan vs enalapril

In-hospital initiation

- Titration algorithm over 8 weeks
- Evaluate biomarker surrogates of efficacy
- Evaluate safety and tolerability
- Explore clinical outcomes
Key Entry Criteria

- Hospitalized for ADHF (signs and symptoms of fluid overload)
- LVEF ≤40% within the last 6 months
- NT-proBNP ≥1600 pg/mL or BNP ≥400 pg/mL (screening)
- Stabilized while still hospitalized
  - In the prior 6 hours:
    - SBP ≥100 mmHg, no symptomatic hypotension
    - No increase in IV diuretics
    - No IV vasodilators
  - In the prior 24 hours: no IV inotropes
Key Endpoints

- **Primary endpoint:** Proportional change in NT-proBNP from baseline to the mean of weeks 4 and 8

- **Safety**
  - Worsening renal function
  - Hyperkalemia
  - Symptomatic hypotension
  - Angioedema

- **Exploratory Clinical Outcomes**
  - Serious clinical composite: death, re-hospitalization for HF, LVAD, or listing for cardiac transplant
  - Expanded composite: Serious composite + addition of HF med, unplanned outpatient IV diuretics or >50% increase in dose
SBP Dose Titration Algorithm

- Starting dose level based on SBP
  - If 100 to <120 mm Hg, sacubitril/valsartan 24/26 mg or enalapril 2.5 mg twice daily
  - If ≥120 mm Hg, sacubitril/valsartan 49/51 mg or enalapril 5 mg twice daily
- Up-titration based on SBP (clinical judgement permitted)
- Target doses
  - sacubitril/valsartan 97/103 mg twice daily or enalapril 10 mg twice daily
## Baseline Characteristics

<table>
<thead>
<tr>
<th></th>
<th>sacubitril/valsartan (n=440)</th>
<th>enalapril (n=441)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Age</strong> (years)</td>
<td>61 (51, 71)</td>
<td>63 (54, 72)</td>
</tr>
<tr>
<td><strong>Women</strong> (%)</td>
<td>25.7</td>
<td>30.2</td>
</tr>
<tr>
<td><strong>Black</strong> (%)</td>
<td>35.9</td>
<td>35.8</td>
</tr>
<tr>
<td><strong>No prior HF diagnosis</strong> (%)</td>
<td>32.3</td>
<td>37.0</td>
</tr>
<tr>
<td><strong>No ACEi/ARB therapy</strong> (%)</td>
<td>52.7</td>
<td>51.5</td>
</tr>
<tr>
<td><strong>LVEF</strong> (*)</td>
<td>0.24 (0.18, 0.30)</td>
<td>0.25 (0.20, 0.30)</td>
</tr>
<tr>
<td><strong>SBP (mm Hg)</strong> (*)</td>
<td>118 (110, 133)</td>
<td>118 (109, 132)</td>
</tr>
<tr>
<td><strong>NT-proBNP (pg/mL)</strong> (*)</td>
<td>2883 (1610, 5403)</td>
<td>2536 (1363, 4917)</td>
</tr>
</tbody>
</table>

*Median (interquartile range).*
Primary Endpoint: % Change in NT-proBNP

29% greater reduction with sacubitril/valsartan
CI 19%, 37%; P < 0.0001
## Safety

<table>
<thead>
<tr>
<th>Safety Events (%)</th>
<th>sacubitril/ valsartan (n=440)</th>
<th>enalapril (n=441)</th>
<th>RR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Worsening renal function*</td>
<td>13.6</td>
<td>14.7</td>
<td>0.93 (0.67-1.28)</td>
</tr>
<tr>
<td>Hyperkalemia†</td>
<td>11.6</td>
<td>9.3</td>
<td>1.25 (0.84-1.84)</td>
</tr>
<tr>
<td>Symptomatic hypotension</td>
<td>15.0</td>
<td>12.7</td>
<td>1.18 (0.85-1.64)</td>
</tr>
<tr>
<td>Angioedema event</td>
<td>1 (0.2%)</td>
<td>6 (1.4%)</td>
<td>0.17 (0.02-1.38)</td>
</tr>
</tbody>
</table>

*Cr ≥0.5 with simultaneous reduction in eGFR of ≥25%
†K+ >5.5 mg/dl

P = NS for all safety events
Serious Composite Clinical Endpoint

Death, HF re-hosp, LVAD, Transplant listing

HR = 0.54; 95% CI 0.37, 0.79
P = 0.001
NNT = 13

Sacubitril/valsartan
N = 440

Enalapril
N = 441

Event Rate (%) vs Days since Randomization

0 7 14 21 28 35 42 49 56

0 10 20
## Exploratory Clinical Endpoints

<table>
<thead>
<tr>
<th></th>
<th>sacubitril/valsartan (n=440)</th>
<th>enalapril (n=441)</th>
<th>HR</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Serious Composite, %</td>
<td>9.3</td>
<td>16.8</td>
<td>0.54</td>
<td>0.001</td>
</tr>
<tr>
<td>Death, %</td>
<td>2.3</td>
<td>3.4</td>
<td>0.66</td>
<td>0.311</td>
</tr>
<tr>
<td>Re-hosp for HF, %</td>
<td>8.0</td>
<td>13.8</td>
<td>0.56</td>
<td>0.005</td>
</tr>
<tr>
<td>LVAD, %</td>
<td>0.2</td>
<td>0.2</td>
<td>0.99</td>
<td>0.999</td>
</tr>
<tr>
<td>Cardiac Transplant, %</td>
<td>0</td>
<td>0</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Expanded Composite*, %</td>
<td>56.6</td>
<td>59.9</td>
<td>0.93</td>
<td>0.369</td>
</tr>
<tr>
<td>Unplanned IV diuretics, %</td>
<td>0.5</td>
<td>0.5</td>
<td>0.99</td>
<td>0.997</td>
</tr>
<tr>
<td>Addition of HF med, %</td>
<td>17.7</td>
<td>19.1</td>
<td>0.92</td>
<td>0.58</td>
</tr>
<tr>
<td>&gt;50% diuretic increase, %</td>
<td>49.6</td>
<td>50.3</td>
<td>0.98</td>
<td>0.812</td>
</tr>
</tbody>
</table>

*Serious composite + addition of HF med, no unplanned outpatient IV diuretics or >50% increase in dose
### Key Subgroup Analyses

#### Change in NT-proBNP

<table>
<thead>
<tr>
<th>Subgroup</th>
<th>sacubitril/valsartan vs. enalapril mean [95% CI]</th>
<th>Subgroup</th>
<th>Hazard Ratio [95% CI]</th>
</tr>
</thead>
<tbody>
<tr>
<td>All Patients</td>
<td>0.71 [0.63, 0.81]</td>
<td>All Patients</td>
<td>0.54 [0.37, 0.79]</td>
</tr>
<tr>
<td>Prior HF</td>
<td></td>
<td>Prior HF</td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>0.65 [0.53, 0.81]</td>
<td>No</td>
<td>0.37 [0.12, 1.15]</td>
</tr>
<tr>
<td>Yes</td>
<td>0.72 [0.63, 0.83]</td>
<td>Yes</td>
<td>0.53 [0.35, 0.80]</td>
</tr>
<tr>
<td>Prior ACEi/ARB</td>
<td></td>
<td>Prior ACEi/ARB</td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>0.72 [0.60, 0.86]</td>
<td>No</td>
<td>0.52 [0.29, 0.95]</td>
</tr>
<tr>
<td>Yes</td>
<td>0.72 [0.61, 0.85]</td>
<td>Yes</td>
<td>0.56 [0.34, 0.92]</td>
</tr>
</tbody>
</table>

Favors sacubitril / valsartan  
Favors enalapril

#### Serious Composite Endpoint

P value (interaction) = NS
Conclusions

Among hemodynamically stabilized acute heart failure patients with reduced EF, compared with enalapril, sacubitril/valsartan administered over 8 weeks …

- Led to greater reduction in NT-proBNP
- Reduced re-hospitalization for heart failure
- Was well tolerated with comparable rates of worsening renal function, hyperkalemia, symptomatic hypotension, and angioedema
These results support the in-hospital initiation of sacubitril/valsartan in stabilized patients with acute decompensated heart failure and reduced EF, irrespective of prior ACEi/ARB use, or prior HF diagnosis.
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Kevin McCague, M.A., Ricardo Rocha, M.D., and Eugene Braunwald, M.D., for
the PIONEER-HF Investigators*