PARADIGM-HF: Are There Any Controversies?

Vijay U. Rao, MD, PhD, FACC, FASE
Franciscan Physician Network
Indiana Heart Physicians
Director, St. Francis Inpatient Heart Failure,
Cardio-Oncology Clinic, Cardiovascular Research, Anti-Coagulation Clinic
Presenter Disclosure Information
PARADIGM-HF: Are There Any Controversies?
Vijay U. Rao, MD, PhD, FACC, FASE

• I am on the speaker’s bureau for BMS, Pfizer, Daichi-Sankyo, Novartis

• I will not discuss off-label or investigational use in my presentation.
LCZ696: A First-in-Class Angiotensin Receptor Neprilysin Inhibitor

Natriuretic Peptide System
- pro BNP
- BNP
- NT-pro BNP
- Inactive fragments
- Neprilysin

Renin-Angiotensin System
- Angiotensinogen (liver secretion)
- Angiotensin I
- Angiotensin II
- AT₁ receptor

Vasodilation
- ↓ blood pressure
- ↓ sympathetic tone
- ↓ aldosterone levels
- ↓ fibrosis
- ↓ hypertrophy
- ↓ natriuresis/diuresis

AHU377
LBQ657
Valsartan

Vasoconstriction
- ↑ blood pressure
- ↑ sympathetic tone
- ↑ aldosterone
- ↑ fibrosis
- ↑ hypertrophy
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*
Prospective comparison of ARNI with ACEI to Determine Impact on Global Mortality and morbidity in Heart Failure trial (PARADIGM-HF)

LCZ696 400 mg daily ↔ Enalapril 20 mg daily

SPECIFICALLY DESIGNED TO REPLACE CURRENT USE OF ACE INHIBITORS AND ANGIOTENSIN RECEPTOR BLOCKERS AS THE CORNERSTONE OF THE TREATMENT OF HEART FAILURE
PARADIGM-HF: Entry Criteria

• NYHA class II-IV heart failure, LV ejection fraction ≤ 40% \(\Rightarrow 35\%\)

• BNP ≥ 150 (or NT-proBNP ≥ 600), but one-third lower if hospitalized for heart failure within 12 months

• Any use of ACE inhibitor or ARB, but able to tolerate stable dose equivalent to at least enalapril 10 mg daily for at least 4 weeks

• Systolic BP ≥ 95 mm Hg, eGFR ≥ 30 ml/min/1.73 m² and serum K ≤ 5.4 mEq/L at randomization
PARADIGM-HF: Study Design

Randomization

Single-blind run-in period

Enalapril 10 mg BID
2 weeks

LCZ696 100 mg BID
1-2 weeks

LCZ696 200 mg BID
2-4 weeks

Double-blind period

LCZ696 200 mg BID
(1:1 randomization)

Enalapril 10 mg BID
<table>
<thead>
<tr>
<th></th>
<th>LCZ696 (n=4187)</th>
<th>Enalapril (n=4212)</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: Cardiovascular Death or Heart Failure Hospitalization (Primary Endpoint)

Kaplan-Meier Estimate of Cumulative Rates (%)

**Enalapril**
(n=4212)

**LCZ696**
(n=4187)

HR = 0.80 (0.73-0.87)
P = 0.0000002
Number needed to treat = 21

Patients at Risk

<table>
<thead>
<tr>
<th></th>
<th>LCZ696</th>
<th>Enalapril</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>4187</td>
<td>4212</td>
</tr>
<tr>
<td>180</td>
<td>3922</td>
<td>3883</td>
</tr>
<tr>
<td>360</td>
<td>3663</td>
<td>3579</td>
</tr>
<tr>
<td>540</td>
<td>3018</td>
<td>2922</td>
</tr>
<tr>
<td>720</td>
<td>2257</td>
<td>2123</td>
</tr>
<tr>
<td>900</td>
<td>1544</td>
<td>1488</td>
</tr>
<tr>
<td>1080</td>
<td>896</td>
<td>853</td>
</tr>
<tr>
<td>1260</td>
<td>249</td>
<td>236</td>
</tr>
</tbody>
</table>
## PARADIGM-HF: Adverse Events

<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</td>
<td>388</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Serum potassium &gt; 6.0 mmol/l</td>
<td>181</td>
<td>236</td>
<td>0.007</td>
</tr>
<tr>
<td>Serum creatinine ≥ 2.5 mg/dl</td>
<td>139</td>
<td>188</td>
<td>0.007</td>
</tr>
<tr>
<td>Cough</td>
<td>474</td>
<td>601</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</td>
<td>9</td>
<td>NS</td>
</tr>
<tr>
<td>Hospitalized; no airway compromise</td>
<td>3</td>
<td>1</td>
<td>NS</td>
</tr>
<tr>
<td>Airway compromise</td>
<td>0</td>
<td>0</td>
<td>----</td>
</tr>
</tbody>
</table>
In heart failure with reduced ejection fraction, when compared with recommended doses of enalapril:

**LCZ696 was more effective than enalapril in . . .**
- Reducing the risk of CV death and HF hospitalization
- Reducing the risk of CV death by *incremental* 20%
- Reducing the risk of HF hospitalization by *incremental* 21%
- Reducing all-cause mortality by *incremental* 16%
- *Incrementally* improving symptoms and physical limitations

**LCZ696 was better tolerated than enalapril . . .**
- Less likely to cause cough, hyperkalemia or renal impairment
- Less likely to be discontinued due to an adverse event
- More hypotension, but no increase in discontinuations
- Not more likely to cause serious angioedema
• **Class I indication:** Inhibition of RAS with ace-inhibitors, OR ARBs, OR ARNI in conjunction with evidence based beta-blockers, and aldosterone antagonists in selected patients is recommended for patients with chronic HFrEF to reduce morbidity and mortality.

• **Class I indication:** In patients with chronic symptomatic HFrEF NYHA class II or III who tolerate an ACE-inhibitor or ARB, replacement by an ARNI is recommended to further reduce morbidity and mortality.
“Straw Man” Comparator

• Were the results seen in PARADIGM-HF merely due to the fact that there was less RAS inhibition with medium dose enalapril (20mg vs 40mg daily) vs maximum dose valsartan (320mg daily)?
  – CONSENSUS (1987), 18mg/day
  – SOLVD-treatment (1991), 17mg/day
  – V-HeFT II (1991), 15mg/day
  – PARADIGM-HF (2014), 18.9mg/day (highest dose of enalapril ever used in a clinical trial)
Run-In Phase of PARADIGM

- PARADIGM had an active run-in phase in which 19.8% of patients dropped out (10.5% in enalapril, 9.3% in entresto). 2/3 of these discontinuations were due to hypotension, hyperkalemia, worsening renal function.
- There are no active run-in phases in the real world setting.
- Run-in phase improves internal validity of results as fewer discontinuations to be expected, but reduce external validity.
- In the randomized population, more patients in the ARNI group experienced symptomatic hypotension (18% vs 12%). Would expect to see considerably more hypotension in the real world setting.
- TITRATION study demonstrated in 498 patients that (76%) patients achieved and maintained sacubitril/valsartan 200 mg twice daily without dose interruption/down-titration over 12 weeks. Also more gradual initiation/uptitration (6 wk vs 3 wk) maximized attainment of target dose in the low-dose ACEI/ARB group (Senni et al. Eur J Heart Fail. 2016 Sep;18(9):1193-202)
### Entresto Dosing

<table>
<thead>
<tr>
<th>Angiotensin-converting enzyme inhibitor (ACEI)</th>
<th>Angiotensin II receptor blocker (ARB)</th>
<th>Not on ACEi or ARB</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Patients receiving a total daily dose of &gt;10 mg of enalapril or therapeutically equivalent doses of another ACEi, for example:</strong></td>
<td><strong>Patients receiving a total daily dose of &gt;160 mg of valsartan or therapeutically equivalent doses of another ARB, for example:</strong></td>
<td><strong>Not currently taking ACEis or ARBs</strong></td>
</tr>
<tr>
<td>- Lisinopril &gt;10 mg</td>
<td>- Losartan &gt;50 mg</td>
<td>- Not currently taking ACEis or ARBs</td>
</tr>
<tr>
<td>- Ramipril &gt;5 mg</td>
<td>- Omesartan &gt;10 mg</td>
<td></td>
</tr>
<tr>
<td><strong>Stop ACEi 36 hours before starting ENTRESTO</strong></td>
<td><strong>Stop ACEi 36 hours before starting ENTRESTO</strong></td>
<td><strong>Start ENTRESTO at the recommended dose of 24/26 mg twice daily</strong></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Start ENTRESTO at the recommended dose of 49/51 mg twice daily</strong></td>
<td><strong>Start ENTRESTO at the recommended dose of 49/51 mg twice daily</strong></td>
<td><strong>Start ENTRESTO at the recommended dose of 24/26 mg twice daily</strong></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Double the dose after 2 to 4 weeks to 49/51 mg twice daily, as tolerated by the patient</strong></td>
<td></td>
<td><strong>Double the dose after 2 to 4 weeks to 49/51 mg twice daily, as tolerated by the patient</strong></td>
</tr>
</tbody>
</table>

### Double the dose of ENTRESTO after 2 to 4 weeks, as tolerated by the patient, to reach the target maintenance dose of 97/103 mg twice daily
Generalizability

- **Patient characteristics:** PARADIGM enrolled a select group of young patients. The mean age was 63 years; 80% were male, and only 6% were black. (How do these data apply to elderly non-Caucasian women?)

- **Lack of NYHA class IV patients:** PARADIGM-HF was a trial with predominately stable (NYHA class II) patients (<1% NYHA class IV patients).
  - despite the label NYHA class II-IV, HF guidelines do not mention NYHA class IV patients, most HF experts have not advocated use of entresto in this population as of yet

- **BP inclusion criteria:** (Mean BP of 120mmHg at baseline on bb and ace-i), when was the last time a low EF patient had that good a blood pressure?
Alzheimer’s Dementia

- Neprilysin is one of multiple enzymes able to degrade amyloid-β (Aβ); its inhibition may increase Aβ levels.
- Aggregable Aβ isoforms are known to accumulate in Alzheimer's disease.
- A theoretical and unproven potential exists that treatment with LCZ696 (angiotensin receptor neprilysin inhibitor) may result in the accumulation of Aβ isoforms.
Alzheimer’s Dementia

• **Animal studies:**
  – Aged, neprilysin knock-out mouse; associated with increased Aβ accumulation in the brain and leads to deposition of amyloid-like structures in vivo as well as with signs of AD-like pathology and with behavioral deficits (Madani et al J Neuroscience Research, Volume 84, Issue 8 December 2006 Pages 1871–1878)
  – Young (2 to 4 years old) cynomolgus monkeys treated with ENTRESTO (24 mg sacubitril/26 mg valsartan/kg/day) for 2 weeks demonstrated increasing CSF Aβ 1-40, 1-42, and 1-38 levels in CSF; there was no corresponding increase in Aβ levels in the brain. In addition, in a toxicology study in cynomolgus monkeys treated with ENTRESTO at 146 mg sacubitril/154 mg valsartan/kg/day for 39-weeks, there was no amyloid-β accumulation in the brain (Entresto Package Insert)

• **Human volunteers:** Once daily LCZ696 (400 mg) for 14 days does not cause changes in CSF levels of aggregable Aβ isoforms 1–42 and 1–40 compared with placebo, despite achieving CSF concentrations sufficient to inhibit neprilysin. The clinical relevance of the increase in CSF Aβ 1–38 is unknown (Langenickel TH Br J Clin Pharmacol. 2016 May; 81(5): 878–890.)

• **Conclusion:** No cognition issues were seen in PARADIGM, but the 2.5-year trial was not designed to assess a problem that may accrue over the long term (long-term extensions studies and PARAGON plan to evaluate this further)
### Table 2. Total Costs, Health Effects, and Incremental Cost-effectiveness Ratio

<table>
<thead>
<tr>
<th></th>
<th>Costs, $</th>
<th>QALYs</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Total</td>
<td>Incremental</td>
</tr>
<tr>
<td>Enalapril</td>
<td>83,303</td>
<td>6.02</td>
</tr>
<tr>
<td>Sacubitril/valsartan</td>
<td>118,815</td>
<td>35,512</td>
</tr>
</tbody>
</table>

**Table Title:**
Total Costs, Health Effects, and Incremental Cost-effectiveness Ratio
Sacubitril/valsartan was cost-effective

- Standard-accepted levels for evaluations of new therapies and interventions (ACC/AHA and World Health Organization)
  - “very good value” (<$50 000 per QALY)
  - “good value” (<$150 000 per QALY)
- ICER for pravastatin before it became generic was $54 000 to $1.4 million per QALY gained
- ICERs for implantable cardioverter defibrillators with and without cardiac resynchronization therapy range from $35 000 to $108 000 per QALY
- ICERs for percutaneous coronary interventions are approximately $36 000 per QALY
- ICER for left ventricular assist devices range from $120 000 to more than $300 000 per QALY gained
Unanswered Questions

- Use in the setting of acute heart failure (ASCEND-HF trial with niseritide) (PIioneer safety change in nt-bnp endpoint)
- Approximate 50% of heart failure patients with HFpEF (PARAGON study)
- Tolerability in large population outside of clinical trial setting
- How to handle symptomatic hypotension
  - cut back on diuretics, stop non-essential bp lower meds such as alpha blockers and nitrates, consider reducing dose of coreg or switching from coreg to toprol xl, holding MRAs during up-titration of entresto
- Effect of Entresto on improvements in myocardial structure and function
- Novartis has announced Fortifying Heart Failure clinical evidence and patient quality of life (FortiHFy): an umbrella clinical program comprising over 40 active or planned trials