Update on PARADIGM-HF
Prospective comparison of ARNI with ACEI to Determine Impact on
Global Mortality and morbidity in Heart Failure trial

Disclosures

- My employer, the University of Glasgow, has been paid by Novartis (who manufacture LCZ696) for my time working as Co-Principal Investigator of the PARADIGM-HF and PARAGON-HF trials.

- Novartis has paid for my travel to and accommodation at meetings connected with these trials and other activities related to LCZ696.

- My employer, the University of Glasgow, has been paid by Novartis for my participation in advisory boards, symposia and other meetings organized by Novartis.
**Angiotensin Receptor Neprilysin Inhibition (ARNI): LCZ696**

- Natriuretic peptides: BK, ADM, Subs-P, VIP, CGRP
- Angiotensin II:
  - Vasoconstriction
  - Sodium/water retention
  - Fibrosis/hypertrophy Degradation products
  - LCZ696 Inhibition (ARNI): LCZ696
  - Vasodilation
  - Natriuresis
  - Diuresis
  - Inhibition of pathologic growth/fibrosis

- Neprilysin
  - Degradation products

- AT₁ Receptor
  - Vasoconstriction
  - Sodium/water retention
  - Fibrosis/hypertrophy
PARADIGM-HF
Prospective comparison of ARNI with ACEI to Determine Impact on Global Mortality and morbidity in Heart Failure trial

Age 64 yr. Female 22%. NYHA class II 70%, III 24%. LVEF 0.29. SBP 122 mmHg. BNP 253 pg/ml (NT pro BNP 1613 pg/ml). eGFR 68 ml/min/1.73m². AF 37%. Prior HF hosp. 62%. Diuretic 80%, digoxin 30%, β-blocker 93%, MRA 56%. ICD 15%. CRT 7%. Average daily dose of enalapril 18.9 mg

Prior ACEi/ARB use discontinued

Outcome driven (CV death): median follow-up = 27 months
PARADIGM-HF: Pre-specified endpoints

- **Primary:** Cardiovascular death or heart failure hospitalization
  - Cardiovascular death
  - Heart failure hospitalization

- **Secondary:**
  - Death from any cause
  - KCCQ (CSS - symptoms and physical limitations)
  - New onset atrial fibrillation
  - Decline in renal function
**PARADIGM-HF**

Prospective comparison of ARNI with ACEI to Determine Impact on Global Mortality and morbidity in Heart Failure trial

**Primary composite outcome**

HR: 0.80 (0.73, 0.87) p = 0.0000004

- Death from CV causes
  - 20% risk reduction

- HF hospitalization
  - 21% risk reduction

McMurray, Packer et al NEJM 2014
PARADIGM-HF: Pre-specified endpoints

- **Primary**: Cardiovascular death or heart failure hospitalization
  - Cardiovascular death
  - Heart failure hospitalization

- **Secondary**:
  - Death from any cause
  - KCCQ (CSS - symptoms and physical limitations)
  - New onset atrial fibrillation
  - Decline in renal function
**PARADIGM-HF**

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**Death from any cause**

16% risk reduction

<table>
<thead>
<tr>
<th>Days after Randomization</th>
<th>Cumulative Proportion of Patients Who Died from Any Cause (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>180</td>
<td>1.55</td>
</tr>
<tr>
<td>360</td>
<td>3.10</td>
</tr>
<tr>
<td>540</td>
<td>4.65</td>
</tr>
<tr>
<td>720</td>
<td>6.19</td>
</tr>
<tr>
<td>900</td>
<td>7.73</td>
</tr>
<tr>
<td>1080</td>
<td>9.27</td>
</tr>
<tr>
<td>1260</td>
<td>10.81</td>
</tr>
</tbody>
</table>

**HR:** 0.84 (0.76, 0.93)

**P = 0.0009**

**Enalapril**
(n=4212)

**LCZ696**
(n=4187)
PARADIGM-HF: Effect of LCZ696 vs. enalapril on other secondary endpoints

<table>
<thead>
<tr>
<th></th>
<th>LCZ696 (n=4187)</th>
<th>Enalapril (n=4212)</th>
<th>Treatment effect</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>KCCQ clinical summary score at 8 months</strong></td>
<td>-2.99 ± 0.36</td>
<td>-4.63 ± 0.36</td>
<td>1.64 (0.63, 2.65)</td>
<td>0.001</td>
</tr>
<tr>
<td><strong>New onset atrial fibrillation</strong></td>
<td>84/2670 (3.1%)</td>
<td>83/2638 (3.1%)</td>
<td>Hazard ratio 0.97 (0.72, 1.31)</td>
<td>0.83</td>
</tr>
<tr>
<td><strong>Protocol-defined decline in renal function</strong>*</td>
<td>94/4187 (2.2%)</td>
<td>108/4212 (2.6%)</td>
<td>Hazard ratio 0.86 (0.65, 1.13)</td>
<td>0.28</td>
</tr>
</tbody>
</table>

*1) ESRD or 2) a decrease ≥50% in eGFR from value at randomization or 3) a decrease in eGFR >30 ml/min/1.73 m² to <60 ml/min/1.73 m²
New data: Pre-specified exploratory outcomes

Selected outcomes – reflecting disease progression
PARADIGM-HF: Percentage of patients with at least 5 points deterioration in KCCQ scores at month 8

Clinical summary score based on the physical limitation and total symptom score domains. Death imputed as zero. The analysis included all patients with at least one KCCQ data point.
## PARADIGM-HF: Physician assessment

### Change in NYHA functional class from baseline to month 8 *(pre-specified time-point)*

<table>
<thead>
<tr>
<th></th>
<th>LCZ696 N=3833* n (%)</th>
<th>Enalapril N=3825* n (%)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Improved</td>
<td>639 (16.7)</td>
<td>569 (14.9)</td>
<td>0.0015</td>
</tr>
<tr>
<td>Unchanged</td>
<td>2989 (78.0)</td>
<td>2990 (78.2)</td>
<td></td>
</tr>
<tr>
<td>Worse</td>
<td>205 (5.4)</td>
<td>266 (7.0)</td>
<td></td>
</tr>
</tbody>
</table>

*Surviving patients with data (deaths excluded)
PARADIGM-HF: Treatment failure*

*Addition of a new drug for treatment of WHF, need for intravenous therapy or increase in diuretic dose >1 month

HR 0.84 (0.74, 0.94)
$p = 0.0029$

Proportion of patients

Enalapril
LCZ696
PARADIGM-HF: Emergency department visits for heart failure†

Proportion of patients

- Enalapril: HR 0.66 (0.52, 0.85)
- LCZ696: HR 0.70 (0.52, 0.94)

Number of ER visits*

- Enalapril: RR 0.70 (0.52, 0.94)
- LCZ696: RR 0.70 (0.52, 0.94)

†Not leading to hospital admission

*Includes repeat episodes
PARADIGM-HF: Hospitalization for heart failure

Proportion of patients

HR 0.79 (0.71, 0.89)

p < 0.0001

Number of admissions*

RR 0.77 (0.67, 0.89)

p = 0.0004

*Includes repeat episodes
### PARADIGM-HF: Intensive care management

#### Intensive management in hospital

<table>
<thead>
<tr>
<th></th>
<th>LCZ696 N=4187 n (%)</th>
<th>Enalapril N=4212 n (%)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of patients requiring intensive care</td>
<td>549 (13.1)</td>
<td>623 (14.8)</td>
<td>0.87 (0.78, 0.98) P=0.019</td>
</tr>
<tr>
<td>Total number of stays in intensive care</td>
<td>768</td>
<td>879</td>
<td>0.82 (0.72, 0.94) P=0.005</td>
</tr>
<tr>
<td>Patients receiving IV positive inotropic drugs</td>
<td>161 (3.8%)</td>
<td>229 (5.4%)</td>
<td>0.69 (0.57, 0.85) P &lt; 0.001</td>
</tr>
</tbody>
</table>
**PARADIGM-HF: Devices and surgery for worsening heart failure**

**Patients with CRT implantation, VAD insertion or heart transplantation**

<table>
<thead>
<tr>
<th></th>
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<th>Enalapril N=4212 n (%)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>CRT</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>• CRT-D</td>
<td>54 (1.3)</td>
<td>77 (1.8)</td>
<td>0.052</td>
</tr>
<tr>
<td>• CRT-P</td>
<td>34 (0.8)</td>
<td>31 (0.7)</td>
<td>0.710</td>
</tr>
<tr>
<td><strong>VAD/transplant</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>• VAD</td>
<td>12 (0.29)</td>
<td>19 (0.45)</td>
<td>0.280</td>
</tr>
<tr>
<td>• Transplant</td>
<td>1 (0.02)</td>
<td>4 (0.09)</td>
<td>0.375</td>
</tr>
</tbody>
</table>
PARADIGM-HF: Hospitalization for any cause

Proportion of patients

HR 0.88 (0.82, 0.94)  
$p < 0.001$

Number of admissions*

RR 0.84 (0.78, 0.91)  
$p < 0.001$

*Includes repeat episodes
PARADIGM-HF: cause/mode of death

All causes | CV causes | Sudden | Worsening HF

<table>
<thead>
<tr>
<th>Number</th>
<th>Enalapril</th>
<th>LCZ696</th>
</tr>
</thead>
<tbody>
<tr>
<td>835</td>
<td>711</td>
<td>693</td>
</tr>
<tr>
<td>558</td>
<td></td>
<td></td>
</tr>
<tr>
<td>311</td>
<td>250</td>
<td></td>
</tr>
<tr>
<td>184</td>
<td>147</td>
<td></td>
</tr>
</tbody>
</table>

HR

<table>
<thead>
<tr>
<th>p</th>
<th>0.84</th>
<th>&lt; 0.001</th>
<th>0.80 0.00008</th>
<th>0.80 0.008</th>
<th>0.79 0.034</th>
</tr>
</thead>
</table>

0.00004

0.00008
Putative placebo analysis

Indirect comparison of LCZ896 with placebo
Putative placebo analysis - comparison network

SOLVD-T

LCZ696

PARADIGM-HF

Enalapril

Placebo

SOLVD-T

CHARM-Alternative

LCZ696

PARADIGM-HF

Candesartan

Placebo

CHARM-Alternative
CV mortality in SOLVD-T, CHARM-Alternative and PARADIGM-HF

**SOLVD-T**
- HR: 0.83 (0.73, 0.95)
- p = 0.008

**CHARM-Alt.**
- HR: 0.85 (0.71, 1.02)
- p = 0.072

**PARADIGM-HF putative placebo**
- from SOLVD-T
  - HR: 0.66 (0.56, 0.79)
  - p < 0.0001
- from CHARM-Alt.
  - HR: 0.68 (0.55, 0.84)
  - p < 0.0001
Heart failure hospitalization in SOLVD-T, CHARM-Alternative and PARADIGM-HF

- SOLVD-T: HR: 0.64 (0.55, 0.73), p < 0.0001
- CHARM-Alt.: HR: 0.68 (0.57, 0.81), p < 0.0001
- PARADIGM-HF putative placebo from SOLVD-T: HR: 0.51 (0.42, 0.61), p < 0.0001
- PARADIGM-HF putative placebo from CHARM-Alt.: HR: 0.54 (0.44, 0.67), p < 0.0001
Summary and conclusions

Compared with enalapril, patients on LCZ696:

- Are less likely to show symptomatic deterioration
- Are less likely to need intensification of oral therapy/addition of iv therapy
- Are less likely to visit the emergency department
- Are less likely to be admitted to hospital
- When admitted, are less likely to go to the ICU and less likely to need iv inotropic therapy
- Are less likely to require devices/surgery for worsening/end-stage heart failure (not statistically significant)
- Are less likely to die prematurely (either suddenly or from worsening HF)
- Less likely to show biomarker evidence of cardiac wall-stress and myocyte injury (data not shown – see Circulation)

Compared with enalapril, LCZ696 slows progression of heart failure, delaying/preventing non-fatal and fatal worsening.
Simultaneous on-line publication

Angiotensin Receptor Neprilysin Inhibition Compared With Enalapril on the Risk of Clinical Progression in Surviving Patients With Heart Failure

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Circulation is available at http://circ.ahajournals.org

A putative placebo analysis of the effects of LCZ696 on clinical outcomes in heart failure

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