Optimal medical treatment today and tomorrow
A PARADIGM change?

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Disclosures

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- Research grants and honoraria from Amgen, Servier
HF: Patho-physiological basis of treatment

Myocardial injury

↓

Left ventricular systolic dysfunction

Systemic vasoconstriction
Renal sodium and water retention

Perceived reduction in circulating volume and pressure

Neurohumoral activation
• SNS
• RAAS
• ET, AVP etc

Left ventricular systolic dysfunction

↓

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Neurohumoral activation
• SNS
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Myocardial injury

↓

Left ventricular systolic dysfunction

Systemic vasoconstriction
Renal sodium and water retention

Perceived reduction in circulating volume and pressure

Neurohumoral activation
• SNS
• RAAS
• ET, AVP etc
Diuretics to relieve symptoms/signs of congestion:

+ ACE inhibitor (or ARB if not tolerated)

ADD a beta-blocker

Still NYHA class II–IV?

Yes

ADD a MR antagonist

Still NYHA class II–IV?

Yes

LVEF ≤ 35%?

Yes

Sinus rhythm and HR ≥ 70 beats/min?

Yes

No

No
The cornerstone of therapy – December 2014

ACE inhibitor (or ARB)
Beta-blocker
MRA
Heart failure: a state of "neurohumoral imbalance"

Vasoconstrictor/anti-natriuretic/pro-mitotic mediators

Vasodilator/natriuretic/anti-mitotic mediators
A paradigm shift: from “neuro-humoral inhibition” to “neuro-humoral modulation”

Vasoconstrictor/anti-natriuretic/pro-mitotic mediators

Vasodilator/natriuretic/anti-mitotic mediators
Natriuretic peptides: How the heart protects itself

- The heart is an endocrine organ
- It secretes A and B type natriuretic peptides into the circulation where they act on the blood vessels, kidneys, adrenal glands, brain etc.
- These peptides protect the heart from volume and pressure overload
Omapatrilat: Dual Inhibitor of ACE and Neprilysin

- Inhibition of carboxypeptidase (ACE)
- Inhibition of endopeptidase (neprilysin)
- Inhibition of aminopeptidase

![Chemical Structure of Omapatrilat](image)
Omapatrilat: Dual Inhibitor of ACE and Neprilysin

- Inhibition of endopeptidase (neprilysin)
- Inhibition of carboxypeptidase (ACE)
- Inhibition of aminopeptidase
Angiotensin Receptor Neprilysin Inhibition (ARNI): LCZ696

- **LCZ696**
  - sacubitril
  - valsartan

**Natriuretic peptides**
- BK, ADM
- Subs-P, VIP, CGRP

- **Vasodilation**
- **Natriuresis**
- **Diuresis**
- **Inhibition of pathologic growth/fibrosis**

**Neprilysin**

- Degradation products

**Angiotensin II**

- **Vasoconstriction**
- **Sodium/water retention**
- **Fibrosis/hypertrophy**

**AT₁ Receptor**
LCZ696: First in class dual-acting angiotensin receptor neprilysin inhibitor

- LCZ696 is a crystalline complex comprised of 6 valsartan moieties, 6 sacubitril (AHU377) moieties, sodium cations, and water held together by network of hydrogen bonds

- Valsartan in LCZ696 is present in anionic form – therefore more bioavailable than in valsartan as a free acid. 200mg of LCZ696 is equivalent to 160mg of standard valsartan
Data Monitoring Committee
H. Dargie (UK) (chair)
R. Foley (US)
G. Francis (US)
M. Komajda (FR)
S. Pocock (UK)

Endpoint and Angioedema Adjudication
S. Solomon (US)
A. Desai (US)
A. Kaplan (US)
N. Brown (US)
B. Zuraw (US)

Executive Committee
J. McMurray (UK) Co-chair
M. Packer (US) Co-chair
J. Rouleau (CA)
S. Solomon (US)
K. Swedberg (SW)
M. Zile (US)

National Leaders

Novartis Operations

Investigative Sites
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*
Patients – main inclusion criteria

- CHF NYHA Class II–IV and LVEF ≤ 40%
  - BNP ≥ 150 pg/ml (NT-proBNP ≥ 600 pg/ml) OR
  - BNP ≥ 100 pg/ml (NT-proBNP ≥ 400 pg/ml) and a hospitalization for HF within the last 12 months

- Must be taking ACEI or ARB: i) dose equivalent to enalapril ≥ 10 mg/d ii) stable dose for at least 4 weeks

- Must be taking a β-blocker: unless contraindicated or not tolerated; stable dose for at least 4 weeks

- MRA (aldosterone antagonist) where indicated: e.g. RALES type patient

- Individually optimized dosing of background HF medications
PARADIGM-HF: Key design issues

- Patients
- Comparators – drug and dose
- Active run-in period
- Primary endpoint and power calculations
Comparators and dose selection: enalapril

Enalapril is the regulatory “gold-standard” ACE inhibitor
• Enalapril is the regulatory “gold-standard” ACE inhibitor: based upon the landmark CONSENSUS (target dose 20mg bid) and SOLVD-T (10mg bid) trials

• Choice of enalapril 10 mg bid rather than 20mg bid as comparator: Mean daily dose of enalapril achieved in SOLVD-T = 16.6mg; in CONSENSUS = 18.4 mg – only 22% achieved target dose.
Comparators and dose selection: LCZ696

- **ARB component**: LCZ696 200 mg bid delivers similar exposures of valsartan as Diovan® 160 mg bid, the dose recommended by international guidelines for treatment of HF and MI (based on Val-HeFT and VALIANT). Lower LCZ696 doses would not deliver evidence-based valsartan exposure.
Blood-pressure reduction with LCZ696, a novel dual-acting inhibitor of the angiotensin II receptor and neprilysin: a randomised, double-blind, placebo-controlled, active comparator study

Luis Miguel Ruilope, Andrej Dukat, Michael Böhm, Yves Lacourcière, Jianjian Gong, Martin P Lefkowitz

Summary
Background LCZ696 is a first-in-class inhibitor of the angiotensin II receptor and neprilysin. We aimed to establish whether the dual actions of LCZ696 lead to further lowering of blood pressure, compared with the angiotensin-receptor blocker valsartan.

Lancet 2010; 375: 1255–66
Published Online
March 16, 2010
LCZ 696: Mean sitting systolic BP reduction

Mean Sitting Systolic BP Reduction:

- **Placebo**: -7.72 mm Hg
- **AHU 200 (neprilysin inhibitor)**: -11.93 mm Hg
- **Valsartan (ARB) 80**: -12.44 mm Hg
- **LCZ 100**: -13.75 mm Hg
- **Valsartan (ARB) 160**: -13.4 mm Hg
- **LCZ 200**: -18.7 mm Hg
- **Valsartan (ARB) 320**: -14.2 mm Hg
- **LCZ 400**: -20.2 mm Hg

**p-values**:
- AHU 200 vs. Placebo: 0.0057
- Valsartan (ARB) 80 vs. Placebo: 0.0006
- LCZ 100 vs. Placebo: 0.4036
- Valsartan (ARB) 160 vs. Placebo: 0.0006
- LCZ 200 vs. Placebo: <0.0001
- Valsartan (ARB) 320 vs. Placebo: <0.0001
- LCZ 400 vs. Placebo: <0.0001
PARADIGM-HF: Active run-in

Single-blind period

Enalapril 5-10 mg bid

LCZ 100 mg bid

LCZ 200 mg bid

1-2 weeks 1-2 weeks 2 weeks

Double-blind period

LCZ696 200 mg BID (n=4187)

N = 8442 (1:1 randomization)

Enalapril 10 mg BID (n=4212)

Outcome driven (CV death): median follow-up = 27 months

Prior ACEi/ARB use discontinued
Rationale for single-blind active run-in design

- Obtain information of tolerability and safety of LCZ696: in view of limited “Phase II” experience

- Maximize the number of patients able to tolerate the target dose of both LCZ696 and enalapril during long-term follow-up: key to testing the hypothesis that LCZ696 200mg bid can beat enalapril 10mg bid. In enalapril arm we must have a mean dose of at least 16.6mg/d.

- We also want to maximize dose of LCZ696 (valsartan and NEP inhibition) to ensure fair comparison.
• **Composite of CV mortality or HF hospitalization**
  - The two most important disease-specific events experienced by patients with systolic heart failure
  - 80% of deaths in patients with systolic HF are cardiovascular
  - HF hospitalization:
    - Reflects progression of the HF syndrome and is the most common cause of hospitalization
    - An ominous development (high subsequent risk of both readmission and death)
    - Main driver of the huge economic burden of HF
Primary endpoint (2)

- Modifiable by effective treatments: ACE inhibitors/ARBs, beta-blockers, aldosterone antagonists and CRT
- Most commonly used primary endpoint in recent/current systolic HF trials: e.g. CHARM, EMPHASIS-HF and SHIFT
A paradigm-shift in treatment

Not adding but replacing

- Replace a current gold standard with something better?
- An ARNI instead of an ACE inhibitor?
Comparators and dose selection: enalapril

- Enalapril is the regulatory “gold-standard” ACE inhibitor: based upon the landmark CONSENSUS (target dose 20mg bid) and SOLVD-T (10mg bid) trials.

- Choice of enalapril 10 mg bid rather than 20mg bid as comparator: Mean daily dose of enalapril achieved in SOLVD-T = 16.6mg; in CONSENSUS = 18.4 mg – only 22% achieved target dose.
## Dose of ACE Inhibitor (enalapril) achieved in randomized outcome trials using forced titration

<table>
<thead>
<tr>
<th>Trial</th>
<th>N</th>
<th>Target dose, mg</th>
<th>Mean daily dose, mg</th>
</tr>
</thead>
<tbody>
<tr>
<td>CONSENSUS (1987)*</td>
<td>127</td>
<td>20 bid</td>
<td>18.4</td>
</tr>
<tr>
<td>SOLVD-T (1991)†</td>
<td>1284</td>
<td>10 bid</td>
<td>16.6</td>
</tr>
<tr>
<td>V-HeFT II (1991)</td>
<td>403</td>
<td>10 bid</td>
<td>15.0</td>
</tr>
<tr>
<td>Network (1998)**</td>
<td>516</td>
<td>10 bid</td>
<td>17.9</td>
</tr>
<tr>
<td>OVERTURE (2002)</td>
<td>2884</td>
<td>10 bid</td>
<td>17.7</td>
</tr>
<tr>
<td>CARMEN (2004)</td>
<td>190 E only</td>
<td>10 bid</td>
<td>16.8</td>
</tr>
<tr>
<td></td>
<td>191 E+Carv</td>
<td>10 bid</td>
<td>14.9</td>
</tr>
<tr>
<td>CIBIS-3 (2005)</td>
<td>190 E first</td>
<td>10 bid</td>
<td>17.2</td>
</tr>
<tr>
<td></td>
<td>191 Bisop first</td>
<td>10 bid</td>
<td>15.8</td>
</tr>
</tbody>
</table>

*22% reached target dose †active run-in; 49% reached target dose **pts had to tolerate test dose of 2.5mg bid
Nt pro BNP and BNP

Cardiomyocyte

Blood

PARADIGM-HF: NT-proBNP and BNP
## PARADIGM-HF: Baseline Characteristics

<table>
<thead>
<tr>
<th></th>
<th>LCZ696 (n=4187)</th>
<th>Enalapril (n=4212)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Age (years)</strong></td>
<td>63.8 ± 11.5</td>
<td>63.8 ± 11.3</td>
</tr>
<tr>
<td><strong>Women (%)</strong></td>
<td>21.0%</td>
<td>22.6%</td>
</tr>
<tr>
<td><strong>Ischemic cardiomyopathy (%)</strong></td>
<td>59.9%</td>
<td>60.1%</td>
</tr>
<tr>
<td><strong>LV ejection fraction (%)</strong></td>
<td>29.6 ± 6.1</td>
<td>29.4 ± 6.3</td>
</tr>
<tr>
<td><strong>NYHA functional class II / III (%)</strong></td>
<td>71.6% / 23.1%</td>
<td>69.4% / 24.9%</td>
</tr>
<tr>
<td><strong>Systolic blood pressure (mm Hg)</strong></td>
<td>122 ± 15</td>
<td>121 ± 15</td>
</tr>
<tr>
<td><strong>Heart rate (beats/min)</strong></td>
<td>72 ± 12</td>
<td>73 ± 12</td>
</tr>
<tr>
<td><strong>N-terminal pro-BNP (pg/ml)</strong></td>
<td>1631 (885-3154)</td>
<td>1594 (886-3305)</td>
</tr>
<tr>
<td><strong>B-type natriuretic peptide (pg/ml)</strong></td>
<td>255 (155-474)</td>
<td>251 (153-465)</td>
</tr>
<tr>
<td><strong>History of diabetes</strong></td>
<td>35%</td>
<td>35%</td>
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<tr>
<td><strong>Digitalis</strong></td>
<td>29.3%</td>
<td>31.2%</td>
</tr>
<tr>
<td><strong>Beta-adrenergic blockers</strong></td>
<td>93.1%</td>
<td>92.9%</td>
</tr>
<tr>
<td><strong>Mineralocorticoid antagonists</strong></td>
<td>54.2%</td>
<td>57.0%</td>
</tr>
<tr>
<td><strong>ICD and/or CRT</strong></td>
<td>21.4%</td>
<td>21.9%</td>
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<td>191 Bisop first</td>
<td>10 bid</td>
<td>15.8</td>
</tr>
<tr>
<td>PARADIGM-HF</td>
<td>4212</td>
<td>10 bid</td>
<td>18.9</td>
</tr>
</tbody>
</table>

† N.B. active run-in; 49% reached target dose. *22% reached target dose
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: Primary outcome
Prospective comparison of ARNI with ACEI to Determine Impact on Global Mortality and morbidity in Heart Failure trial

At risk
Enalapril: 4212 3883 3579 2922 2123 1488 853 236
LCZ696: 4187 3922 3663 3018 2257 1544 896 249

HR: 0.80 (0.73, 0.87)
\( p = 0.0000004 \)

McMurray et al. NEJM 2014
PARADIGM-HF: Primary outcome
KM-curves first 30 days

Hazard ratio 0.60 (0.38-0.94)
P = 0.027

Enalapril
(n=4212)

LCZ696
(n=4187)

Days After Randomization

Patients at Risk
LCZ696 4187 4174 4153 4140
Enalapril 4212 4192 4166 4143

Packer et al  Circ 2014
PARADIGM-HF: Pre-specified endpoints

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

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  - 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

Death from CV causes 20% risk reduction

HF hospitalization 21% risk reduction

Death from CV causes 20% risk reduction

HF hospitalization 21% risk reduction

McMurray et al  NEJM 2014
PARADIGM-HF: Hospitalization for HF

**Proportion of patients**
- HR 0.79 (0.71, 0.89)
- p < 0.0001

**Number of admissions**
- RR 0.77
- p = 0.0004

- McMurray et al. NEJM 2014
- Packer et al. Circ 2014
Subgroups

Eighteen pre-defined subgroups
**PARADIGM-HF: Sub-group analysis (primary endpoint and CV death)**

<table>
<thead>
<tr>
<th>Subgroup</th>
<th>LCZ696 No.</th>
<th>ENA-Pril No.</th>
<th>Hazard Ratio (95% CI)</th>
<th>P Value for Interaction</th>
<th>CV Death</th>
<th>P Value for Interaction</th>
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<tbody>
<tr>
<td>All Patients</td>
<td>4187</td>
<td>4212</td>
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<td>Age &lt;65 yr</td>
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<td>2168</td>
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<td>Age ≥65 yr</td>
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<td>2044</td>
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<td>0.32</td>
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<td>0.62</td>
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<td>Age &gt;75 yr</td>
<td>3403</td>
<td>3433</td>
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<td>0.32</td>
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<td>Sex Male</td>
<td>3308</td>
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<td>0.63</td>
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<td>Sex Female</td>
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<td>953</td>
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<td>0.58</td>
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<td>Race White</td>
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<td>Race Black</td>
<td>213</td>
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<td>Race Asian</td>
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<td>Race Other</td>
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<td>Region Asia-Pacific</td>
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<td>742</td>
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<td>NYHA class I or II</td>
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<td>0.03</td>
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<td>NYHA class III or IV</td>
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<td>Estimated GFR &lt;60 ml/min/1.73 m²</td>
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<td>1520</td>
<td>2646</td>
<td>2692</td>
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<td>Diabeties No</td>
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<td>Diabeties Yes</td>
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<td>Systolic blood pressure sMedian</td>
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<td>Systolic blood pressure &gt;Median</td>
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<td>2275</td>
<td>1948</td>
<td>1936</td>
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<td>Ejection fraction sMedian</td>
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<td>0.36</td>
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<td>Ejection fraction &gt;55%</td>
<td>472</td>
<td>489</td>
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<td>Atrial fibrillation No</td>
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<tr>
<td>NT-proBNP sMedian</td>
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<tr>
<td>NT-proBNP &gt;Median</td>
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<td>2087</td>
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<td>Hypertension No</td>
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<tr>
<td>Hypertension Yes</td>
<td>2960</td>
<td>2971</td>
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<tr>
<td>Prior use of ACE inhibitor No</td>
<td>921</td>
<td>946</td>
<td>3266</td>
<td>3266</td>
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<td>2271</td>
<td>2400</td>
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<td>0.32</td>
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<td>Prior hospitalization for heart failure No</td>
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<td>2607</td>
<td>2567</td>
<td>0.10</td>
<td>0.19</td>
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<tr>
<td>Prior hospitalization for heart failure Yes</td>
<td>1275</td>
<td>1248</td>
<td>1621</td>
<td>1631</td>
<td>0.27</td>
<td>0.21</td>
</tr>
<tr>
<td>Time since diagnosis of heart failure 1 y</td>
<td>1251</td>
<td>1242</td>
<td>1621</td>
<td>1613</td>
<td>1291</td>
<td>1355</td>
</tr>
</tbody>
</table>

McMurray 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
Death from any cause
16% risk reduction

HR: 0.84 (0.76, 0.93)
p < 0.0001

McMurray et al  NEJM 2014
PARADIGM-HF: cause/mode of death

<table>
<thead>
<tr>
<th></th>
<th>All causes</th>
<th>CV causes</th>
<th>Sudden</th>
<th>WHF</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number</td>
<td>835</td>
<td>683</td>
<td>311</td>
<td>184</td>
</tr>
<tr>
<td>HR p-value</td>
<td>0.84</td>
<td>0.80</td>
<td>0.80</td>
<td>0.79</td>
</tr>
<tr>
<td></td>
<td>&lt;0.0001</td>
<td>0.00004</td>
<td>0.008</td>
<td>0.04</td>
</tr>
</tbody>
</table>

McMurray et al AHA 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: 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 (3.2%)</td>
<td>83/2638 (3.2%)</td>
<td>Hazard ratio 0.97 (0.72, 1.31)</td>
<td>0.84</td>
</tr>
<tr>
<td><strong>Protocol-defined decline in renal function</strong></td>
<td>94/4187 (2.3%)</td>
<td>108/4212 (2.6%)</td>
<td>Hazard ratio 0.86 (0.65, 1.13)</td>
<td>0.28</td>
</tr>
</tbody>
</table>

*McMurray et al NEJM 2014*
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

<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>Improved</td>
<td>639 (15.8)</td>
<td>569 (14.0)</td>
<td>0.0003</td>
</tr>
<tr>
<td>Unchanged</td>
<td>2989 (74.1)</td>
<td>2990 (73.6)</td>
<td></td>
</tr>
<tr>
<td>Worse*</td>
<td>407 (10.1)</td>
<td>504 (12.4)</td>
<td></td>
</tr>
</tbody>
</table>

*2-sided. Patients who died were included in the worse category.
New data

Exploratory outcomes
PARADIGM-HF: Hospitalization for any cause

Proportion of patients

HR 0.88 (0.82, 0.94)
\( p = 0.0001 \)

Number of admissions

RR 0.85 (0.78, 0.91)
\( p = 0.0004 \)

Packer et al Circ 2014
PARADIGM-HF: Hospitalization for any cause

Rate ratio 0.77 (0.67-0.89)
P < 0.001

Cumulative Number of Hospitalizations for Heart Failure per 100 Patients

Days After Randomization

Patients at Risk

<table>
<thead>
<tr>
<th></th>
<th>LCZ696</th>
<th>Enalapril</th>
</tr>
</thead>
<tbody>
<tr>
<td>n</td>
<td>4187</td>
<td>4212</td>
</tr>
<tr>
<td>180</td>
<td>4054</td>
<td>4049</td>
</tr>
<tr>
<td>360</td>
<td>3857</td>
<td>3857</td>
</tr>
<tr>
<td>540</td>
<td>3276</td>
<td>3228</td>
</tr>
<tr>
<td>720</td>
<td>2472</td>
<td>2408</td>
</tr>
<tr>
<td>900</td>
<td>1710</td>
<td>1724</td>
</tr>
<tr>
<td>1080</td>
<td>1001</td>
<td>993</td>
</tr>
<tr>
<td>1260</td>
<td>279</td>
<td>278</td>
</tr>
<tr>
<td>1440</td>
<td>12</td>
<td>17</td>
</tr>
</tbody>
</table>

Packer et al Circ 2014
PARADIGM-HF: ER visits for HF

- Proportion of patients
  - HR 0.66 (0.52, 0.85)
  - \( p = 0.001 \)

- Number of ER visits
  - RR 0.70 (0.52, 0.94)
  - \( p = 0.017 \)

Packer et al. Circ 2014
Safety

Pre-defined safety assessments
PARADIGM-HF: Systolic BP

Mean difference (LCZ-Ena): -2.70 (-3.07, -2.34)(mmHg)
p-value: < 0.001
## PARADIGM-HF: Safety

<table>
<thead>
<tr>
<th></th>
<th>LCZ696 (n=4187)</th>
<th>Enalapril (n=4212)</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Hypotension (%)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>symptoms</td>
<td>14.0</td>
<td>9.2</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>symptoms and SBP &lt; 90 mmHg</td>
<td>2.7</td>
<td>1.4</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td><strong>Renal impairment (%)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cr ≥ 2.5 mg/dl</td>
<td>3.3</td>
<td>4.5</td>
<td>0.007</td>
</tr>
<tr>
<td>Cr ≥ 3.0 mg/dl</td>
<td>1.5</td>
<td>2.0</td>
<td>0.10</td>
</tr>
<tr>
<td><strong>Hyperkalaemia (%)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>K⁺ &gt; 5.5 mmol/l</td>
<td>16.2</td>
<td>17.4</td>
<td>0.15</td>
</tr>
<tr>
<td>K⁺ &gt; 6.0 mmol/l</td>
<td>4.3</td>
<td>5.6</td>
<td>0.007</td>
</tr>
<tr>
<td><strong>Cough (%)</strong></td>
<td>11.3</td>
<td>14.3</td>
<td>&lt; 0.001</td>
</tr>
</tbody>
</table>
PARADIGM-HF: Adverse events leading to permanent study drug discontinuation

- Any adverse event: p = 0.03
- Hypotension: p = 0.38
- Renal reasons: p = 0.002
- Hyperkalaemia: p = 0.56
<table>
<thead>
<tr>
<th></th>
<th>LCZ696 (n=4187)</th>
<th>Enalapril (n=4212)</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Not hospitalized</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No treatment/antihistamines n, (%)</td>
<td>10 (0.2)</td>
<td>5 (0.1)</td>
<td>0.19</td>
</tr>
<tr>
<td>Catecholamines/corticosteroids n, (%)</td>
<td>6 (0.1)</td>
<td>4 (0.1)</td>
<td>0.52</td>
</tr>
<tr>
<td><strong>Hospitalized</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No airway compromise n, (%)</td>
<td>3 (0.1)</td>
<td>1 (0.0)</td>
<td>0.31</td>
</tr>
<tr>
<td>Airway compromise n, (%)</td>
<td>0 (0.0)</td>
<td>0 (0.0)</td>
<td>-</td>
</tr>
</tbody>
</table>
### Do we need to do another trial to obtain regulatory approval/change clinical practice?

<table>
<thead>
<tr>
<th>Number of trials with $P &lt; 0.05$ showing efficacy</th>
<th>$P$ value required in a single trial to provide same strength of evidence</th>
<th>PARADIGM-HF: Effect on primary endpoint</th>
<th>PARADIGM-HF: Effect on cardiovascular death</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>0.05</td>
<td></td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>0.00125</td>
<td></td>
<td>0.00008</td>
</tr>
<tr>
<td>3</td>
<td>0.00003125</td>
<td></td>
<td>0.000008</td>
</tr>
<tr>
<td>4</td>
<td>0.00000078</td>
<td></td>
<td>0.0000004</td>
</tr>
<tr>
<td>5</td>
<td>0.000000195</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Based on formula $(0.025)^n \times 2$ (personal communication Stuart Pocock)
The consistent benefits of LCZ696 on all outcomes in HF

Compared with enalapril, patients on LCZ696:

- Have prolonged survival
- Are less likely to show symptomatic deterioration with a need to become hospitalised
- Show less deterioration in renal function which characteristically worsens over time in heart failure
- Are less likely to die prematurely (either suddenly or from worsening HF)
HF-REF: The building blocks of therapy

- Beta-blocker
- ACEI/ARB
- MRA
- CABG
- Digoxin
- Ivabradine
- H-ISDN
HF-REF: The building blocks of therapy

- Beta-blocker
- ARNI
- MRA
- ICD
- CRT
- VAD
- Tx
- Digoxin
- CABG
- Ivabradine
- H-ISDN
- MRA