Feast after Famine: The New Drugs for the Treatment of Heart Failure

Maria Rosa Costanzo, M.D., F.A.C.C., F.A.H.A., F.E.S.C.
Medical Director, Advocate Medical Group-Midwest Heart Specialists Heart Failure and Pulmonary Arterial Hypertension Programs
Medical Director, Edward Hospital Center for Advanced Heart Failure
The History of Heart Failure Therapy

1898
Tigerstedt discovers
injection of renal cortex extract into rabbits ↑BP (renin)

1940
Goldblatt discovers renin catalyzes formation of A1

1956
Kisch discovers granules in the atrium

1959
Discovery of spironolactone

1965
Venom of Brazilian viper inhibits kininase which degrades bradykinin and ACE

1970
Marshall discovers 1st ARB, IV saralazine which ↓BP

1974
ACE Teprotide IV ↓ renal vasoconstriction, ↓BP and improves HF hemodynamics

1977
Ondetti synthesizes captopril

1978
De Bold finds that atrial granules store polypeptide

1978
Rat atria extracts ↑Na excretion 30 folds and urine volume 10 folds

1981
BURNETT reports elevated ANP in HF

1981
Rat atria extracts ↑Na excretion 30 folds and urine volume 10 folds

1985
Heart established as an endocrine organ

1987
CONSENSUS Trial

1985
The Pfeffers show that captopril reduces LV remodeling after MI

1986
Sudoh discovers BNP

1988
Sudoh discovers CNP

1988
Sudoh discovers BNP is produced by the ventricles

1989
Sudoh discovers CNP

1991
Sudoh discovers BNP

1977
Ondetti synthetizes captopril

1981
BURNETT reports elevated ANP in HF

1985
Heart established as an endocrine organ

1985
The Pfeffers show that captopril reduces LV remodeling after MI

1989
Sudoh discovers CNP

1991
Sudoh discovers BNP

1999
RALES trial

2001
Val-HeFT Trial

2001-present
NP markers of HF presence and prognosis

2011
ASCEND trial

1956
Kisch discovers granules in the atrium

1959
Discovery of spironolactone

1978
De Bold finds that atrial granules store polypeptide

1981
BURNETT reports elevated ANP in HF

1985
Heart established as an endocrine organ

1987
CONSENSUS Trial

1988
Sudoh discovers BNP

1989
Sudoh discovers CNP

1991
Sudoh discovers BNP

1999
RALES trial

2001-present
NP markers of HF presence and prognosis

2011
ASCEND trial

1956
Kisch discovers granules in the atrium

1959
Discovery of spironolactone

1978
De Bold finds that atrial granules store polypeptide

1981
BURNETT reports elevated ANP in HF

1985
Heart established as an endocrine organ

1987
CONSENSUS Trial

1988
Sudoh discovers BNP

1989
Sudoh discovers CNP

1991
Sudoh discovers BNP

1999
RALES trial

2001-present
NP markers of HF presence and prognosis

2011
ASCEND trial
Neprilsyn Is Not New

1974
Kerr & Kenny
Discover Neutral Endopeptidase in the proximal tubule of rabbit kidney

1974
Stephenson & Kelly
Discover that NEP is a strong hydrolyzer of ANP

1980
Roques synthesizes thiorphan, a NEPi

1980
Ksander & Lisy
discover sacubitril
and show ↓ diuresis and ↓ Aldo in sheep model of pacing-induced HF

1987
Fournier-Zaluski
discovers orally-active NEP

1987
Seymour
shows that combination of NEPi and captopril ↓ BP in rats more than each drug alone

1988
NEP degrades Bradykinin AII, ET-1 Oxytocin Opioid peptides Substance P Gastrin VIP Amyloid β protein

1991
Ksander & Lisy
Discover sacubitril

1994
Fournier-Zaluski
Discover orally-active NEPi

1995
Seymour
shows that combination of NEPi and captopril ↓ BP in rats more than each drug alone

1998
NEP degrades Bradykinin AII, ET-1 Oxytocin Opioid peptides Substance P Gastrin VIP Amyloid β protein

2000
IMPRESS trial (573)
Strong trend toward benefit of omapatrilat vs. lisinopril in HF

2003
Webb & Ksander
Invent LCZ696 (valsartan+sacubitril)

2004
Ksander & Lisy
Discover sacubitril

2004
OCTAVE trial (25,302)
Omapatrilat vs. Enalapril Better BP control More angioedema (2.17% vs. 0.68%)

2005
IMPRESS trial (573)
Strong trend toward benefit of omapatrilat vs. lisinopril in HF

2007
LCZ696 vs. valsartan 1,328 HTN pts

2012
PARAMOUNT trial

2012
PARAMOUNT trial

2012
PARAMOUNT trial

2012
PARAMOUNT trial
Evidence-Based HFrEF RCTs

All pharmacologic Therapies Have Focused on Neurohormonal Blockade

Blue = ACEI
Green = ARB
Red = MRA
Yellow = BB
From: The Path to an Angiotensin Receptor Antagonist-Neprilysin Inhibitor in the Treatment of Heart Failure

Cardiac injury/overload

HFpEF

↑SNS

β blockers

↑Renin

ACE inhibitors

Angiotensinogen

↑Ang I

ACE inhibition

Bradykinin degradation

↑Ang II

NEP

NEPi

NPRA

↑ANP/BNP

↑NPS/Wall stress

Angiotensin II receptor blockers (ARB)

AT1R

MRCA

Vasoconstriction

Proliferation

↑ROS

↑Fibrosis

Aldosterone

Na retention

Vasodilation

↓Fibrosis

Natriuresis

LCZ 696

From: The Path to an Angiotensin Receptor Antagonist-Neprilysin Inhibitor in the Treatment of Heart Failure

Complementary Blood Pressure Lowering with NEP inhibition and ARB

Mean Sitting **Systolic** BP Reduction: Placebo-subtracted

<table>
<thead>
<tr>
<th>Treatment</th>
<th>BP Reduction (mm Hg)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>AHU 200</td>
<td>-4.2</td>
<td>&lt;0.006</td>
</tr>
<tr>
<td>Vals 80</td>
<td>-4.7</td>
<td>0.404</td>
</tr>
<tr>
<td>LCZ 100</td>
<td>-6.0</td>
<td></td>
</tr>
<tr>
<td>Vals 160</td>
<td>-5.7</td>
<td>0.0006</td>
</tr>
<tr>
<td>LCZ 200</td>
<td>-11.0</td>
<td></td>
</tr>
<tr>
<td>Vals 320</td>
<td>-6.4</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>LCZ 400</td>
<td>-12.5</td>
<td></td>
</tr>
</tbody>
</table>

Placebo effect = -7.72 mmHg

n = 154 to 172 / group

Valsartan, LCZ 696, AHU 377 (sacubitril)

J Am Coll Cardiol. 2015;65(10):1029-1041. doi:10.1016/j.jacc.2015.01.033
Primary results of the PARAMOUNT trial in patients with HFpEF

J Am Coll Cardiol. 2015;65(10):1029-1041. doi:10.1016/j.jacc.2015.01.033
PARADIGM-HF Study Design

Screening Criteria, Run-in Periods, and Randomization.

10,513 Patients entered enalapril run-in phase (median duration, 13 days; IQR, 14–21)
- 1,102 Discontinued study
  - 591 (5.6%) Had adverse event
  - 66 (0.6%) Had abnormal laboratory or other test result
  - 171 (1.6%) Withdrew consent
  - 138 (1.3%) Had protocol deviation, had administrative problem, or were lost to follow-up
  - 49 (0.5%) Died
  - 87 (0.8%) Had other reasons

9,419 Entered LCZ696 run-in phase (median duration, 29 days; IQR, 26–35)
- 977 Discontinued study
  - 547 (5.8%) Had adverse event
  - 58 (0.6%) Had abnormal laboratory or other test result
  - 100 (1.1%) Withdrew consent
  - 146 (1.6%) Had protocol deviation, had administrative problem, or were lost to follow-up
  - 47 (0.5%) Died
  - 79 (0.8%) Had other reasons

8,442 Underwent randomization
- 43 Were excluded
  - 6 Did not undergo valid randomization
  - 37 Were from four sites prematurely closed because of major GCP violations

4,187 Were assigned to receive LCZ696
  - 4,176 Had known final vital status
  - 11 Had unknown final vital status

4,212 Were assigned to receive enalapril
  - 4,203 Had known final vital status
  - 9 Had unknown final vital status

## Characteristics of the Patients at Baseline

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>LCZ696 (N=4187)</th>
<th>Enalapril (N=4212)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age — yr</td>
<td>63.8±11.5</td>
<td>63.8±11.3</td>
</tr>
<tr>
<td>Female sex — no. (%)</td>
<td>879 (21.0)</td>
<td>953 (22.6)</td>
</tr>
<tr>
<td>Race or ethnic group — no. (%)†</td>
<td></td>
<td></td>
</tr>
<tr>
<td>White</td>
<td>2763 (66.0)</td>
<td>2781 (66.0)</td>
</tr>
<tr>
<td>Black</td>
<td>215 (5.1)</td>
<td>215 (5.1)</td>
</tr>
<tr>
<td>Asian</td>
<td>759 (18.1)</td>
<td>750 (17.8)</td>
</tr>
<tr>
<td>Other</td>
<td>452 (10.8)</td>
<td>466 (11.1)</td>
</tr>
<tr>
<td>Region — no. (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>North America</td>
<td>310 (7.4)</td>
<td>292 (6.9)</td>
</tr>
<tr>
<td>Latin America</td>
<td>713 (17.0)</td>
<td>720 (17.1)</td>
</tr>
<tr>
<td>Western Europe and other‡</td>
<td>1026 (24.5)</td>
<td>1025 (24.3)</td>
</tr>
<tr>
<td>Central Europe</td>
<td>1393 (33.3)</td>
<td>1433 (34.0)</td>
</tr>
<tr>
<td>Asia-Pacific</td>
<td>745 (17.8)</td>
<td>742 (17.6)</td>
</tr>
<tr>
<td>Systolic blood pressure — mm Hg</td>
<td>122±15</td>
<td>122±15</td>
</tr>
<tr>
<td>Heart rate — beats/min</td>
<td>72±12</td>
<td>73±12</td>
</tr>
<tr>
<td>Body-mass index§</td>
<td>28.1±5.3</td>
<td>28.2±5.5</td>
</tr>
<tr>
<td>Serum creatinine — mg/dl</td>
<td>1.13±0.3</td>
<td>1.12±0.3</td>
</tr>
<tr>
<td>Clinical features of heart failure</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ischemic cardiomyopathy — no. (%)</td>
<td>2506 (59.9)</td>
<td>2530 (60.1)</td>
</tr>
<tr>
<td>Left ventricular ejection fraction — %</td>
<td>29.6±4.6</td>
<td>29.4±4.6</td>
</tr>
<tr>
<td>Median B-type natriuretic peptide (IQ9) — pg/ml</td>
<td>255 (155–474)</td>
<td>251 (153–465)</td>
</tr>
<tr>
<td>Median N-terminal pro-B-type natriuretic peptide (IQ9) — pg/ml</td>
<td>1631 (885–3154)</td>
<td>1594 (886–3055)</td>
</tr>
<tr>
<td>NYHA functional class — no. (%)§</td>
<td></td>
<td></td>
</tr>
<tr>
<td>I</td>
<td>180 (4.3)</td>
<td>209 (5.0)</td>
</tr>
<tr>
<td>II</td>
<td>2998 (71.6)</td>
<td>2921 (69.3)</td>
</tr>
<tr>
<td>III</td>
<td>969 (23.1)</td>
<td>1049 (24.9)</td>
</tr>
<tr>
<td>IV</td>
<td>33 (0.8)</td>
<td>27 (0.6)</td>
</tr>
<tr>
<td>Missing data</td>
<td>7 (0.2)</td>
<td>6 (0.1)</td>
</tr>
<tr>
<td>Medical history — no. (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hypertension</td>
<td>2969 (70.0)</td>
<td>2971 (70.5)</td>
</tr>
<tr>
<td>Diabetes</td>
<td>1451 (34.7)</td>
<td>1456 (34.6)</td>
</tr>
<tr>
<td>Atrial fibrillation</td>
<td>1517 (36.2)</td>
<td>1574 (37.4)</td>
</tr>
<tr>
<td>Hospitalization for heart failure</td>
<td>2607 (62.3)</td>
<td>2667 (65.3)</td>
</tr>
<tr>
<td>Myocardial infarction</td>
<td>1818 (43.4)</td>
<td>1816 (43.1)</td>
</tr>
<tr>
<td>Stroke</td>
<td>355 (8.5)</td>
<td>370 (8.8)</td>
</tr>
<tr>
<td>Pretrial use of ACE inhibitor</td>
<td>3266 (78.0)</td>
<td>3266 (77.5)</td>
</tr>
<tr>
<td>Pretrial use of ARB†</td>
<td>929 (22.2)</td>
<td>965 (22.9)</td>
</tr>
<tr>
<td>Treatments at randomization — no. (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diuretic</td>
<td>3363 (80.3)</td>
<td>3375 (80.1)</td>
</tr>
<tr>
<td>Digitalis</td>
<td>1223 (29.2)</td>
<td>1316 (31.2)</td>
</tr>
<tr>
<td>Beta-blocker</td>
<td>3899 (93.1)</td>
<td>3912 (92.9)</td>
</tr>
<tr>
<td>Mineralocorticoid antagonist</td>
<td>2271 (54.2)</td>
<td>2400 (57.0)</td>
</tr>
<tr>
<td>Implantable cardioverter-defibrillator</td>
<td>623 (14.9)</td>
<td>620 (14.7)</td>
</tr>
<tr>
<td>Cardiac resynchronization therapy</td>
<td>292 (7.0)</td>
<td>282 (6.7)</td>
</tr>
</tbody>
</table>
Kaplan–Meier Curves for Key Study Outcomes, According to Study Group.

**A Primary End Point**
- Hazard ratio, 0.80 (95% CI, 0.73–0.87)
- P<0.001

**B Death from Cardiovascular Causes**
- Hazard ratio, 0.80 (95% CI, 0.71–0.89)
- P<0.001

**C Hospitalization for Heart Failure**
- Hazard ratio, 0.79 (95% CI, 0.71–0.89)
- P<0.001

**D Death from Any Cause**
- Hazard ratio, 0.84 (95% CI, 0.76–0.93)
- P<0.001

### Primary and Secondary Outcomes.

<table>
<thead>
<tr>
<th>Outcome</th>
<th>LCZ696 (N = 4187)</th>
<th>Enalapril (N = 4212)</th>
<th>Hazard Ratio or Difference (95% CI)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Primary composite outcome — no. (%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Death from cardiovascular causes or first hospitalization for worsening heart failure</td>
<td>914 (21.8)</td>
<td>1117 (26.5)</td>
<td>0.80 (0.73–0.87)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Death from cardiovascular causes</td>
<td>558 (13.3)</td>
<td>693 (16.5)</td>
<td>0.80 (0.71–0.89)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>First hospitalization for worsening heart failure</td>
<td>537 (12.8)</td>
<td>658 (15.6)</td>
<td>0.79 (0.71–0.89)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Secondary outcomes — no. (%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Death from any cause</td>
<td>711 (17.0)</td>
<td>835 (19.8)</td>
<td>0.84 (0.76–0.93)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Change in KCCQ clinical summary score at 8 mo†</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>New-onset atrial fibrillation‡</td>
<td>84 (3.1)</td>
<td>83 (3.1)</td>
<td>0.97 (0.72–1.31)</td>
<td>0.83</td>
</tr>
<tr>
<td>Decline in renal function‡</td>
<td>94 (2.2)</td>
<td>108 (2.6)</td>
<td>0.86 (0.65–1.13)</td>
<td>0.28</td>
</tr>
</tbody>
</table>

### Pre-specified Subgroup Analyses

<table>
<thead>
<tr>
<th>Subgroup</th>
<th>LC2996</th>
<th>Enelapril Better</th>
</tr>
</thead>
<tbody>
<tr>
<td>All patients</td>
<td>4187</td>
<td>4212</td>
</tr>
<tr>
<td><strong>Age</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;65 yr</td>
<td>2311</td>
<td>2168</td>
</tr>
<tr>
<td>â‰¥ 65 yr</td>
<td>2016</td>
<td>2044</td>
</tr>
<tr>
<td><strong>Estimated GFR</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&gt;45 mg/ml/1.73 m²</td>
<td>3458</td>
<td>3633</td>
</tr>
<tr>
<td>â‰¥ 45 mg/ml/1.73 m²</td>
<td>374</td>
<td>776</td>
</tr>
<tr>
<td><strong>Diabetes</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>1740</td>
<td>2056</td>
</tr>
<tr>
<td>Yes</td>
<td>1511</td>
<td>1316</td>
</tr>
<tr>
<td><strong>Systolic blood pressure</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;140 mmHg</td>
<td>2298</td>
<td>2299</td>
</tr>
<tr>
<td>â‰¥ 140 mmHg</td>
<td>1689</td>
<td>1913</td>
</tr>
<tr>
<td><strong>Ejection fraction</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;0.50</td>
<td>2239</td>
<td>2275</td>
</tr>
<tr>
<td>â‰¥ 0.50</td>
<td>1685</td>
<td>1936</td>
</tr>
<tr>
<td><strong>Hypertension</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>2670</td>
<td>2638</td>
</tr>
<tr>
<td>Yes</td>
<td>1517</td>
<td>1574</td>
</tr>
<tr>
<td><strong>Previous use of ACE inhibitors</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>1128</td>
<td>1241</td>
</tr>
<tr>
<td>Yes</td>
<td>2069</td>
<td>2971</td>
</tr>
<tr>
<td><strong>Prior use of aldosterone antagonists</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>1916</td>
<td>1812</td>
</tr>
<tr>
<td>Yes</td>
<td>2271</td>
<td>2400</td>
</tr>
<tr>
<td><strong>Prior hospitalization for heart failure</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>1380</td>
<td>1545</td>
</tr>
<tr>
<td>Yes</td>
<td>2607</td>
<td>2867</td>
</tr>
</tbody>
</table>

## Primary Endpoint

<table>
<thead>
<tr>
<th>Hazard ratio (95% CI)</th>
<th>P-value for interaction</th>
<th>Hazard ratio (95% CI)</th>
<th>P-value for interaction</th>
</tr>
</thead>
<tbody>
<tr>
<td>All patients</td>
<td></td>
<td>0.47</td>
<td></td>
</tr>
<tr>
<td>&lt;65 yr</td>
<td></td>
<td>0.70</td>
<td></td>
</tr>
<tr>
<td>â‰¥ 65 yr</td>
<td></td>
<td>0.32</td>
<td>0.62</td>
</tr>
<tr>
<td>&lt;75 yr</td>
<td></td>
<td>0.63</td>
<td>0.02</td>
</tr>
<tr>
<td>â‰¥ 75 yr</td>
<td></td>
<td>0.58</td>
<td>0.88</td>
</tr>
<tr>
<td>Male</td>
<td></td>
<td>0.37</td>
<td>0.81</td>
</tr>
<tr>
<td>Female</td>
<td></td>
<td>0.37</td>
<td>0.81</td>
</tr>
<tr>
<td>Black</td>
<td></td>
<td>0.37</td>
<td>0.81</td>
</tr>
<tr>
<td>Others</td>
<td></td>
<td>0.37</td>
<td>0.81</td>
</tr>
<tr>
<td>Systolic blood pressure</td>
<td></td>
<td>0.63</td>
<td>0.02</td>
</tr>
<tr>
<td>&lt;140 mmHg</td>
<td></td>
<td>0.39</td>
<td>0.16</td>
</tr>
<tr>
<td>Hypertension</td>
<td></td>
<td>0.25</td>
<td>1.00</td>
</tr>
<tr>
<td>Yes</td>
<td></td>
<td>0.16</td>
<td>0.13</td>
</tr>
<tr>
<td>No</td>
<td></td>
<td>0.87</td>
<td>0.14</td>
</tr>
<tr>
<td>Prior use of ACE inhibitors</td>
<td></td>
<td>0.08</td>
<td>0.06</td>
</tr>
<tr>
<td>Yes</td>
<td></td>
<td>0.10</td>
<td>0.32</td>
</tr>
<tr>
<td>No</td>
<td></td>
<td>0.10</td>
<td>0.19</td>
</tr>
<tr>
<td>Time since diagnosis of heart failure</td>
<td></td>
<td>0.27</td>
<td>0.21</td>
</tr>
</tbody>
</table>
Table 3. Adverse Events during Randomized Treatment.*

<table>
<thead>
<tr>
<th>Event</th>
<th>LCZ696 (N=4187)</th>
<th>Enalapril (N=4212)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hypotension</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Symptomatic</td>
<td>588 (14.0)</td>
<td>388 (9.2)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Symptomatic with systolic blood pressure &lt;90 mm Hg</td>
<td>112 (2.7)</td>
<td>59 (1.4)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Elevated serum creatinine</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>≥2.5 mg/dl</td>
<td>139 (3.3)</td>
<td>188 (4.5)</td>
<td>0.007</td>
</tr>
<tr>
<td>≥3.0 mg/dl</td>
<td>63 (1.5)</td>
<td>83 (2.0)</td>
<td>0.10</td>
</tr>
<tr>
<td>Elevated serum potassium</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&gt;5.5 mmol/liter</td>
<td>674 (16.1)</td>
<td>727 (17.3)</td>
<td>0.15</td>
</tr>
<tr>
<td>&gt;6.0 mmol/liter</td>
<td>181 (4.3)</td>
<td>236 (5.6)</td>
<td>0.007</td>
</tr>
<tr>
<td>Cough</td>
<td>474 (11.3)</td>
<td>601 (14.3)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Angioedema†</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No treatment or use of antihistamines only</td>
<td>10 (0.2)</td>
<td>5 (0.1)</td>
<td>0.19</td>
</tr>
<tr>
<td>Use of catecholamines or glucocorticoids without hospitalization</td>
<td>6 (0.1)</td>
<td>4 (0.1)</td>
<td>0.52</td>
</tr>
<tr>
<td>Hospitalization without airway compromise</td>
<td>3 (0.1)</td>
<td>1 (&lt;0.1)</td>
<td>0.31</td>
</tr>
<tr>
<td>Airway compromise</td>
<td>0</td>
<td>0</td>
<td>—</td>
</tr>
</tbody>
</table>

# Mean Baseline Characteristics of Patients with Heart Failure and a Reduced Ejection Fraction in Five Trials

<table>
<thead>
<tr>
<th>Trial</th>
<th>Age</th>
<th>%</th>
<th>NYHA Class</th>
<th>Heart Rate</th>
<th>Systolic Blood Pressure</th>
<th>Treatment</th>
<th>ICD with or without CRT</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>yr</td>
<td>%</td>
<td>% of patients</td>
<td>beats/min</td>
<td>mm Hg</td>
<td>ACE Inhibitor or ARB</td>
<td>Beta-Blocker</td>
</tr>
<tr>
<td>AHEFT</td>
<td>57</td>
<td>24</td>
<td>95 in class III</td>
<td>NA</td>
<td>126</td>
<td>87</td>
<td>74</td>
</tr>
<tr>
<td>MADIT-CRT</td>
<td>65</td>
<td>24</td>
<td>85 in class II</td>
<td>NA</td>
<td>122</td>
<td>97</td>
<td>93</td>
</tr>
<tr>
<td>SHIFT</td>
<td>60</td>
<td>29</td>
<td>49 in class II; 50 in class III</td>
<td>79</td>
<td>121</td>
<td>91</td>
<td>89</td>
</tr>
<tr>
<td>EMPHASIS-HF</td>
<td>68</td>
<td>26</td>
<td>100 in class II</td>
<td>72</td>
<td>124</td>
<td>93</td>
<td>86</td>
</tr>
<tr>
<td>PARADIGM-HF</td>
<td>64</td>
<td>&lt;35</td>
<td>(in 88% of patients)</td>
<td>70 in class II; 24 in class III</td>
<td>72</td>
<td>121</td>
<td>100</td>
</tr>
</tbody>
</table>

Numbers of Patients with Heart Failure Who Would Need to Be Treated to Reduce Any-Cause Mortality in Seven Clinical Trials.

Kaplan–Meier curve for the time to first hospitalization for heart failure during first 30 days after randomization, according to study group.

Milton Packer et al. Circulation. 2015;131:54-61

Hazard ratio 0.60 (0.38-0.94)
P = 0.027

Enalapril
(n=4212)

LCZ696
(n=4187)

K-M Estimate of Cumulative Rate

Patients at Risk

<table>
<thead>
<tr>
<th></th>
<th>LCZ696</th>
<th>Enalapril</th>
</tr>
</thead>
<tbody>
<tr>
<td>4187</td>
<td>4174</td>
<td>4153</td>
</tr>
<tr>
<td>4212</td>
<td>4192</td>
<td>4166</td>
</tr>
<tr>
<td></td>
<td></td>
<td>4140</td>
</tr>
<tr>
<td></td>
<td></td>
<td>4143</td>
</tr>
</tbody>
</table>

Copyright © American Heart Association, Inc. All rights reserved.
Cumulative number of hospitalizations for heart failure in the enalapril and LCZ696 groups per 100 patients.

Milton Packer et al. Circulation. 2015;131:54-61
### HF Subgroups Who May Be a Challenge to the Implementation of LCZ69s in Clinical Practice

<table>
<thead>
<tr>
<th>Clinical Characteristics</th>
<th>Low Blood Pressure</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hospitalization for HF</td>
<td></td>
</tr>
<tr>
<td>NYHA IV</td>
<td></td>
</tr>
<tr>
<td>Advanced HF</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Drug Therapy-Related Characteristics</th>
<th>ACEi naïve patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>Low ACEi dose</td>
<td></td>
</tr>
<tr>
<td>High ACEi dose</td>
<td></td>
</tr>
<tr>
<td>Patients on ARB therapy</td>
<td></td>
</tr>
</tbody>
</table>

Filippatos G et al. BMC Medicine 2015; 13: 35-8
Neprilysin is one of more than 20 enzymes that modulates removal of $\text{A} \beta$ peptides.

A 2-week study in normal volunteers involving healthy human volunteers did not show an increase in $\text{A} \beta$ levels.

Cognitive function was similar in LCZ696 and enalapril groups.

This will be specifically studied in PARAGON.

Neprilysin degrades the amyloid $\beta$ protein and protects against Alzheimer’s disease.

Neprilysin inhibits prostate cancer cells invasion in vitro.

Neprilysin overexpression improved disease-free survival in women with breast cancer.

Concerns

PARADIGM’s Investigators Answers

Neprilysin is one of more than 20 enzymes that modulates removal of $\text{A} \beta$ peptides.

A 2-week study in normal volunteers involving healthy human volunteers did not show an increase in $\text{A} \beta$ levels.

Cognitive function was similar in LCZ696 and enalapril groups.

This will be specifically studied in PARAGON.
Concerns

- PARADIGM had few patients with ICD (15%) and CRT (7%)
- Average HR was 72 bpm suggesting suboptimal beta-blockade

PARADIGM’s Investigators Answers

- ICD/CRT were implanted in 54% of PARADIGM’s North America Population.
- The benefits of LCZ696 were consistent across geographical areas and benefit occurred regardless of the presence or absence of ICD/CRT
- In PARADIGM, approximately 50% of the patients received 50% or more of the target dose of BB and LCZ696 benefit occurred regardless of baseline HR or BB dose
“the Data Monitoring Committee unanimously recommended early closure of the PARADIGM-HF

[Prospective comparison of ARNi with ACEi to Determine Impact on Global Mortality and morbidity in HF trial],

indicating patients with chronic heart failure with reduced ejection fraction [HFrEF] who received LCZ696 lived longer without being hospitalized for heart failure than those who received standard care with [angiotensin-converting enzyme] inhibitor [ACEi] enalapril.

**Based on the compelling efficacy and primary endpoint having been met, the trial will now close early**

Heart Rate in Cardiovascular Pathophysiology

Heart Rate ↑

- Atherosclerosis
  - Oxidative Stress ↑
  - Plaque Stability ↓
  - Arterial Stiffness ↑
- Ischemia
  - Oxygen Consumption ↑
  - Diastole length ↓
  - Coronary Perfusion ↓
- Chronic Heart Failure
  - TICM
    - Oxygen Demand ↑
    - Ventricular Efficiency ↓
    - Ventricular relaxation ↓
- Remodeling
  - LVH ↑
- Comorbidities
  - Microalbuminuria ↑

Reil JC, Böhm M. Curr Opin Cardiol 2013; 28:326-31
HR and Mortality in *HEALTHY* Men

Jouven X et al. NEJM 2005; 352: 1951-8
HR and Mortality in CAD

Diaz A et al. Eur Heart J 2005; 26: 967-74
HR Reduction and Mortality after MI

Kiekshus JK et al. Am J Cardiol 1986; 43F-49F
Resting Heart Rate in Heart Failure

Fox K et al. J Am Coll Cardiol. 2007;50(9):823-830
The $I_f$ Current Is the Largest Contribution to Diastolic Depolarization

Mechanism Of Action of Ivabradine

SHIFT Trial: Study Design

7411 patients assessed

7106 selected*

305 excluded because of non-compliance with study criteria

548 excluded
- 349 non-compliance with study criteria
- 125 withdrew consent
- 68 adverse event
- 5 missing
- 1 no randomisation call

6558 randomised

3268 assigned ivabradine

27 excluded
- 2 study drug not dispensed
- 25 patients from removed centres

3241 analysed (including 2 lost to follow-up and 73 who withdrew consent for study participation)

3290 assigned placebo

26 excluded
- 5 study drug not dispensed
- 21 patients from removed centres

3264 analysed (including 1 lost to follow-up and 58 who withdrew consent for study participation)

Svedberg K et al. Lancet 2010; 376: 875-85
SHIFT Trial: Baseline Characteristics

Age: 60.4 years
Male sex: 77%
HR: 79.8 BPM
LVEF: 29%
NYHA:
   II 49%
   III 50%
IHD: 67.5%
Non-IHD: 32.5%
Hx of AF: 8%
GDMT
   Digoxin: 22%
   β-blockers: 90%
CRT: 1%
ICD: 3%

Swedberg K et al. Lancet 2010; 376: 875-85
## Effects of Ivabradine on Primary and Major Secondary Endpoints

Swedberg K et al. Lancet 2010; 376: 875-85

<table>
<thead>
<tr>
<th>Endpoint</th>
<th>Ivabradine group (n=3241)</th>
<th>Placebo group (n=3264)</th>
<th>HR (95% CI)</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Primary endpoint</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cardiovascular death or hospital admission for worsening heart failure</td>
<td>793 (24%)</td>
<td>937 (29%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Mortality endpoints</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>All-cause mortality</td>
<td>503 (16%)</td>
<td>552 (17%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cardiovascular mortality</td>
<td>449 (14%)</td>
<td>491 (15%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Death from heart failure</td>
<td>113 (3%)</td>
<td>151 (5%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Other endpoints</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>All-cause hospital admission</td>
<td>1231 (38%)</td>
<td>1356 (42%)</td>
<td>0.89 (0.82-0.96)</td>
<td>0.003</td>
</tr>
<tr>
<td>Hospital admission for worsening heart failure</td>
<td>514 (16%)</td>
<td>672 (21%)</td>
<td>0.74 (0.66-0.83)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Any cardiovascular hospital admission</td>
<td>977 (30%)</td>
<td>1122 (34%)</td>
<td>0.85 (0.78-0.92)</td>
<td>0.0002</td>
</tr>
<tr>
<td>Cardiovascular death, or hospital admission for worsening heart failure, or hospital admission for non-fatal myocardial infarction</td>
<td>825 (25%)</td>
<td>979 (30%)</td>
<td>0.82 (0.74-0.89)</td>
<td>&lt;0.0001</td>
</tr>
</tbody>
</table>

Data are number of first events (%), hazard ratio (HR; 95% CI), and p values.

18% ↓ in the primary endpoint

26% ↓ in death from HF
Effect of Ivabradine on Primary Composite End-Point in Pre-Specified Subgroups

Swedberg K et al. Lancet 2010; 376: 875-85

Ivabradine helped those who needed help!!!
Baseline Resting HR and Risk of CV Mortality or Hospital Admission for HF, 1st HF Hospitalization and CV Mortality in the Placebo Group of the SHIFT Trial

The Higher the Heart Rate, The Greater the Risk of Bad Outcomes!!!
...And this Is Why Baseline HR Influences the Effects of Ivabradine on Outcomes!

Effects of Ivabradine on LV Remodeling and Function: SHIFT Echocardiographic Substudy

## Selected Serious Adverse Events

<table>
<thead>
<tr>
<th>Patients with an adverse event</th>
<th>Ivabradine group (n=3232)</th>
<th>Placebo group (n=3260)</th>
<th>p value</th>
<th>Patients with an adverse event leading to drug withdrawal</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Ivabradine group (n=3232)</td>
</tr>
<tr>
<td>All</td>
<td>2439 (75%)</td>
<td>2423 (74%)</td>
<td>0.303</td>
<td>467 (14%)</td>
</tr>
<tr>
<td>Heart failure</td>
<td>804 (25%)</td>
<td>937 (29%)</td>
<td>0.0005</td>
<td>70 (2%)</td>
</tr>
<tr>
<td>Symptomatic bradycardia</td>
<td>150 (5%)</td>
<td>32 (1%)</td>
<td>&lt;0.0001</td>
<td>20 (1%)</td>
</tr>
<tr>
<td>Asymptomatic bradycardia</td>
<td>184 (6%)</td>
<td>48 (1%)</td>
<td>&lt;0.0001</td>
<td>28 (1%)</td>
</tr>
<tr>
<td>Atrial fibrillation</td>
<td>306 (9%)</td>
<td>251 (8%)</td>
<td>0.012</td>
<td>135 (4%)</td>
</tr>
<tr>
<td>Phosphenes*</td>
<td>89 (3%)</td>
<td>17 (1%)</td>
<td>&lt;0.0001</td>
<td>7 (&lt;1%)</td>
</tr>
<tr>
<td>Blurred vision</td>
<td>17 (1%)</td>
<td>7 (&lt;1%)</td>
<td>0.042</td>
<td>1 (&lt;1%)</td>
</tr>
</tbody>
</table>

Swedberg K et al. Lancet 2010; 376: 875-85
Relationship between ivabradine treatment and cardiovascular outcomes in patients with stable CAD and LVSD with limiting angina: a subgroup analysis of the BEAUTIFUL trial

Composite Primary End-Point (CV Death or Hosp. for Fatal or Non-Fatal MI)

A

Limiting angina

Composite primary endpoint
HR (95% CI), 0.76 (0.58–1.00), P = 0.05

B

Limiting angina and heart rate ≥ 70 b.p.m.

Composite primary endpoint
HR (95% CI), 0.69 (0.47–1.01), P = 0.06

Hospitalization for Fatal and Non-Fatal MI

A

Limiting angina

Hospitalization for fatal and non-fatal MI
HR (95% CI), 0.58 (0.37–0.92), P = 0.021

B

Limiting angina and heart rate ≥ 70 b.p.m.

Hospitalization for fatal and non-fatal MI
HR (95% CI), 0.27 (0.11–0.66), P = 0.002

Fox K et al. EHJ 2009: 30: 2337–45
Analysis of Randomized Controlled Trials on the Effect of Magnitude of Heart Rate Reduction on Clinical Outcomes in Patients With Systolic Chronic Heart Failure Receiving Beta-Blockers

19,537 patients from 9 BB trials (BEST, CIBIS, CIBIS II, CIBIS III, COMET, COPERNICUS, MERIT-HF, SENIORS, US Carvedilol HF study)

Flannery G et al. AJC 2008; 101: 865-9
Effects on Outcomes of Heart Rate Reduction by Ivabradine in Patients With Congestive Heart Failure: Is There an Influence of Beta-Blocker Dose?: Findings From the SHIFT (Systolic Heart failure treatment with the I_{	ext{f}} inhibitor ivabradine Trial) Study

Considerations on Ivabradine

- Increased HR itself has multiple detrimental CV effects
- A correlation between HR and mortality is unequivocally present in healthy individuals, and patients with CAD, MI and HF
- Ivabradine interferes with the $I_f$ current, which is the principal contributor to diastolic depolarization
- In chronic HF patients with HR >70 bpm, Ivabradine reduces the combined end-point of CV death and HF hosp. by 18%, HF death by 26%, and all-cause hosp. by 11%
- These benefits were achieved in the whole population and across pre-specified subgroups
- All Ivabradine RCTs have consistently shown that the drug is safe
- The benefits of Ivabradine may be independent of those afforded by beta blockers
Conclusions

• In randomized clinical trials both valsartan-sacubitril and ivabradine have been shown to have effectiveness and acceptable safety in the populations that were studied.

• There is uncertainty about how the 2 new drugs will be positioned in the upcoming update of the AHA/ACC Guidelines on the management of HF in the adult.

• The main questions remaining on valsartan-sacubitril are:
  • Efficacy in ACEI/ARB-naïve populations
  • Efficacy in patients on high dose ACEI/ARB
  • Effects in acutely decompensated HF
  • Effects on mental status changes
  • Cost

• The main questions remaining on ivabradine are
  • Lack of efficacy in patients with AF
  • Concern about increase in the rates of de-novo AF
  • Efficacy in patients on high-dose beta-blockers
  • Efficacy in patients with CAD and LV systolic dysfunction

• My message: Let’s rejoice in these advances and gain experience with the use of these new drugs in clinical practice!!!
I beg you to read this:

Unbelievable Folly of Clinical Trials in Heart Failure
The Inconvenient Truth About How Investigators and Guidelines Weigh Evidence

Packer M. Circ Heart Fail 2016; 9:e002837. DOI: 10.1161/circheartfailure.116.002837.