Midwest Heart Failure Quarterly Webinar
September 9th, 2015
12 - 1PM CST

1-800-988-9553 • Passcode: 2449375
**Audience:** All parties interested in improving HF care including, but not limited to: nurses, HF program coordinators, cardiologists, program medical directors, quality improvement personnel

**Purpose:** Engage in educational opportunities, network and share best practice to improve HF patient care

**Meeting Schedule:** One hour quarterly meetings

**Next meeting:** November 18th, 12-1pm CST
MIDWEST HEART FAILURE QUARTERLY WEBINAR

Wednesday, November 18, 2015
12-1PM CST

Presentation: Enhancing Your Skills in HF Quality Improvement & Data Analysis
Beth Chojnacki
Aurora St. Luke’s Medical Center, Milwaukee, WI

Join us for:
- Best practices
- Data review
- Updates
- New topics every quarter

Register online today!
www.surveymonkey.com/r/MidwestHeartFailureWebinarNovember
Registration begins at 7:30 AM
Breakfast and lunch are included. No cost to attend but advanced registration is required.

Advance your knowledge of:
Coordinator Role
Data Analysis for Quality Improvement
Patient Education
And more!

Register online today!
www.surveymonkey.com/s/HeartFailureBootCamp
Presentation: Clinical Implications of Entresto

Clyde W. Yancy, MD, MSc, MACC, FAHA, MACP
Northwestern University, Feinberg School of Medicine
Northwestern Memorial Hospital
DISCLOSURES

• Consultant/speaker/honoraria: none

• Editorial Boards: American Heart Journal, American Journal of Cardiology -associate editor; Circulation; Circulation-Heart Failure; Journal of the American College of Cardiology- associate editor (HF)

• Guideline writing committees: Chair, ACC/AHA, chronic HF; member, atrial fibrillation; Chair, Performance Measures, Sudden Cardiac Death

• Federal appointments: FDA: Immediate Past Chair, Cardiovascular Device Panel; ad hoc consultant; NIH – Scientific Management and Review Board for the Director; AHRQ- adhoc consultant; NHLBI- consultant; PCORI- methodology committee member

• Volunteer Appointments: American Heart Association-President, American Heart Association, 2009-2010; American College of Cardiology, Founder- CREDO
Pharmacological Treatment for Stage C HF/REF; an update, 2015

Clyde W. Yancy, MD, MSc
Vice-Dean, Diversity & Inclusion
Chief of Cardiology
Magerstadt Professor of Medicine
Professor, Medical Social Sciences
Northwestern University, Feinberg School of Medicine
&
Associate Director,
Bluhm Cardiovascular Institute
Northwestern Memorial Hospital
Chicago, IL
**Stages, Phenotypes and Treatment of HF**

**STAGE A**
At high risk for HF but without structural heart disease or symptoms of HF

- e.g., Patients with:
  - HTN
  - Atherosclerotic disease
  - DM
  - Obesity
  - Metabolic syndrome
  - Patients Using cardiotoxins
  - With family history of cardiomyopathy

**THERAPY**
- Goals
  - Heart healthy lifestyle
  - Prevent vascular, coronary disease
  - Prevent LV structural abnormalities
- Drugs
  - ACEI or ARB in appropriate patients for vascular disease or DM
  - Statins as appropriate

**STAGE B**
Structural heart disease but without signs or symptoms of HF

- e.g., Patients with:
  - Previous MI
  - LV remodeling including LVH and low EF
  - Asymptomatic valvular disease

**THERAPY**
- Goals
  - Prevent HF symptoms
  - Prevent further cardiac remodeling
- Drugs
  - ACEI or ARB as appropriate
  - Beta blockers as appropriate
- In selected patients
  - ICD
  - Revascularization or valvular surgery as appropriate

**STAGE C**
Structural heart disease with prior or current symptoms of HF

- e.g., Patients with:
  - Known structural heart disease and HF signs and symptoms

**THERAPY**
- Goals
  - Control symptoms
  - Improve HRQOL
  - Prevent hospitalization
  - Prevent mortality
- Drugs for routine use
  - Diuretics for fluid retention
  - ACEI or ARB
  - Beta blockers
  - Aldosterone antagonists
- Drugs for use in selected patients
  - Hydralazine/isosorbide dinitrate
  - ACEI and ARB
  - Digoxin
- In selected patients
  - CRT
  - ICD
  - Revascularization or valvular surgery as appropriate

**STAGE D**
Refractory HF

- e.g., Patients with:
  - Marked HF symptoms at rest
  - Recurrent hospitalizations despite GDMT

**THERAPY**
- Goals
  - Control symptoms
  - Improve HRQOL
  - Reduce hospital readmissions
  - Establish patient’s end-of-life goals
- Options
  - Advanced care measures
  - Heart transplant
  - Chronic inotropes
  - Temporary or permanent MCS
  - Experimental surgery or drugs
  - Palliative care and hospice
  - ICD deactivation
Pharmacologic Treatment for Stage C HFrEF

HFrEF Stage C
NYHA Class I – IV

Treatment:

For NYHA class II-IV patients. Provided estimated creatinine >30 mL/min and K+ <5.0 mEq/dL

Class I, LOE A
ACEI or ARB AND Beta Blocker

For persistently symptomatic African Americans, NYHA class III-IV

Add

Class I, LOE A
Hydral-Nitrates

For all volume overload, NYHA class II-IV patients

Add

Class I, LOE C
Loop Diuretics

For NYHA class II-IV patients. Provided estimated creatinine >30 mL/min and K+ <5.0 mEq/dL

Add

Class I, LOE A
Aldosterone Antagonist
Drugs That Reduce Mortality in Heart Failure With Reduced Ejection Fraction

Drugs that inhibit the renin-angiotensin system have modest effects on survival.

Based on results of SOLVD-Treatment, CHARM-Alternative, COPERNICUS, MERIT-HF, CIBIS II, RALES and EMPHASIS-HF.
Medical Therapy for Stage C HFrEF: Magnitude of Benefit Demonstrated in RCTs

<table>
<thead>
<tr>
<th>GDMT</th>
<th>RR Reduction in Mortality</th>
<th>NNT for Mortality Reduction (Standardized to 36 mo)</th>
<th>RR Reduction in HF Hospitalizations</th>
</tr>
</thead>
<tbody>
<tr>
<td>ACE inhibitor or ARB</td>
<td>17%</td>
<td>26</td>
<td>31%</td>
</tr>
<tr>
<td>Beta blocker</td>
<td>34%</td>
<td>9</td>
<td>41%</td>
</tr>
<tr>
<td>Aldosterone antagonist</td>
<td>30%</td>
<td>6</td>
<td>35%</td>
</tr>
<tr>
<td>Hydralazine/nitrate</td>
<td>43%</td>
<td>7</td>
<td>33%</td>
</tr>
</tbody>
</table>

Fonarow, G, ... Yancy, C. American Heart Journal, 2012
LESSON #1: current evidence –based medical therapy is effective in reduced EF heart failure
The newest “Paradigms” in HF
Simplified schematic of the renin–angiotensin–aldosterone system.

Simplified schematic of the natriuretic peptide system (NPS).

Cardiac antiremodeling effects of angiotensin receptor neprilysin inhibitors (ARNi) in vitro and in vivo.

Neprilysin Inhibition Potentiates Actions of Endogenous Vasoactive Peptides That Counter Maladaptive Mechanisms in Heart Failure

**Endogenous vasoactive peptides**
(natriuretic peptides, adrenomedullin, bradykinin, substance P, calcitonin gene-related peptide)

<table>
<thead>
<tr>
<th>Neprilysin inhibition</th>
</tr>
</thead>
<tbody>
<tr>
<td>Neurohormonal activation</td>
</tr>
<tr>
<td>Vascular tone</td>
</tr>
<tr>
<td>Cardiac fibrosis, hypertrophy</td>
</tr>
<tr>
<td>Sodium retention</td>
</tr>
</tbody>
</table>

Inactive metabolites
Mechanisms of Progression in Heart Failure

Myocardial or vascular stress or injury

Increased activity or response to maladaptive mechanisms

Decreased activity or response to adaptive mechanisms

Angiotensin receptor blocker

Inhibition of neprilysin

Evolution and progression of heart failure
LESSON #2: sufficient biological plausibility exists to warrant a shift in current treatment paradigms and to target neprilysin
Comparison of Omapatrilat and Enalapril in Patients With Chronic Heart Failure


Circulation
Volume 106(8):920-926
August 20, 2002
Figure 1. Kaplan-Meier analysis of time to death or hospitalization for heart failure requiring intravenous treatment in the omapatrilat and enalapril groups.

Angiotensin Receptor Neprilysin Inhibition (ARNI): LCZ696
Dual angiotensin receptor and neprilysin inhibition as an alternative to angiotensin-converting enzyme inhibition in patients with chronic systolic heart failure: rationale for and design of the Prospective comparison of ARNI with ACEI to Determine Impact on Global Mortality and morbidity in Heart Failure trial (PARADIGM-HF)

John J. V. McMurray, Milton Packer, Akshay S. Desai, Jim Gong, Martin P. Lefkowitz, Adel R. Rizkala, Jean Rouleau, Victor C. Shi, Scott D. Solomon, Karl Swedberg, Michael R. Zile, and on behalf of the PARADIGM-HF Committees and Investigators†
PARADIGM-HF: Entry Criteria

• NYHA class II-IV heart failure

• LV ejection fraction ≤ 40% ➔ 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

• Guideline-recommended use of beta-blockers and mineralocorticoid receptor antagonists

• Systolic BP ≥ 95 mm Hg, eGFR ≥ 30 ml/min/1.73 m² and serum K ≤ 5.4 mEq/L at randomization
PARADIGM-HF study schema.
LESSON #3: PARADIGM HF study design; open label run-in followed by double blind RCT.

- 20% failed to progress to RCT
- 10% due to inability to tolerate full dose ACE-I
- 10% due to inability to tolerate full dose LCZ-696
- this experience more likely approximates what you will experience in clinical practice

- the ideal candidate for LCZ-696 is stable, mostly NYHA class II, on reasonable dose of ACE-I and has an adequate blood pressure; has been exposed to appropriate evidence based HFrEF
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
Prospective comparison of ARNI with ACEI to Determine Impact on Global Mortality and morbidity in Heart Failure trial

Death from any cause
16% risk reduction

HR: 0.84 (0.76, 0.93)
P = 0.0009
Prespecified Subgroup Analyses.

<table>
<thead>
<tr>
<th>Subgroup</th>
<th>LCZ696</th>
<th>Enalapril</th>
<th>Primary End Point</th>
<th>Death from Cardiovascular Causes</th>
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</thead>
<tbody>
<tr>
<td></td>
<td>no</td>
<td></td>
<td>Hazard Ratio</td>
<td>P-value for interaction</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>(95% CI)</td>
<td></td>
</tr>
<tr>
<td>All patients</td>
<td>4187</td>
<td>4212</td>
<td>0.47</td>
<td>0.70</td>
</tr>
<tr>
<td>Age</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>&lt;65 yr</td>
<td>2111</td>
<td>2168</td>
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<tr>
<td>≥65 yr</td>
<td>2076</td>
<td>2044</td>
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<td>Age</td>
<td>3403</td>
<td>3433</td>
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<td>&gt;75 yr</td>
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<td>779</td>
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<td>Sex</td>
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<tr>
<td>Male</td>
<td>3308</td>
<td>3259</td>
<td>0.63</td>
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<td>Female</td>
<td>876</td>
<td>953</td>
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<td>Race</td>
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<td>2781</td>
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<td>White</td>
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<td>Asian</td>
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<td>Native American</td>
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<td>Other</td>
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<td>Region</td>
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<td>North America</td>
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<td>Latin America</td>
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<td>Western Europe and other</td>
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<td>Central Europe</td>
<td>1393</td>
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<td>Asia–Pacific</td>
<td>745</td>
<td>742</td>
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<td>NYHA class</td>
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<td>I or II</td>
<td>3178</td>
<td>3130</td>
<td>0.03</td>
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<td>III or IV</td>
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<td>Estimated GFR</td>
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<tr>
<td>&lt;60 ml/min/1.73 m²</td>
<td>1541</td>
<td>1520</td>
<td>0.91</td>
<td>0.73</td>
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<td>≥60 ml/min/1.73 m²</td>
<td>2646</td>
<td>2692</td>
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<td>Diabetes</td>
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<td>2756</td>
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<td>Yes</td>
<td>1451</td>
<td>1456</td>
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<td>Systolic blood pressure</td>
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<td>≤Median</td>
<td>2298</td>
<td>2299</td>
<td>0.87</td>
<td>0.62</td>
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<tr>
<td>&gt;Median</td>
<td>1889</td>
<td>1913</td>
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<tr>
<td>Ejection fraction</td>
<td></td>
<td></td>
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<tr>
<td>=Median</td>
<td>2239</td>
<td>2275</td>
<td>0.71</td>
<td>0.80</td>
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<tr>
<td>&gt;Median</td>
<td>1948</td>
<td>1936</td>
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<tr>
<td>Ejection fraction</td>
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<tr>
<td>≤35%</td>
<td>3715</td>
<td>3722</td>
<td>0.36</td>
<td>0.36</td>
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<tr>
<td>&gt;35%</td>
<td>472</td>
<td>489</td>
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<tr>
<td>Atrial fibrillation</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>No</td>
<td>2670</td>
<td>2638</td>
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<td>Yes</td>
<td>1517</td>
<td>1574</td>
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<tr>
<td>NT-proBNP</td>
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<td>=Median</td>
<td>2079</td>
<td>2116</td>
<td>0.16</td>
<td>0.33</td>
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<tr>
<td>&gt;Median</td>
<td>2103</td>
<td>2087</td>
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<tr>
<td>Hypertension</td>
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<tr>
<td>No</td>
<td>1218</td>
<td>1241</td>
<td>0.87</td>
<td>0.14</td>
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<td>Yes</td>
<td>2969</td>
<td>2971</td>
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<tr>
<td>Prior use of ACE inhibitor</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>921</td>
<td>946</td>
<td>0.09</td>
<td>0.06</td>
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<td>Yes</td>
<td>3266</td>
<td>3266</td>
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<tr>
<td>Prior use of aldosterone antagonist</td>
<td></td>
<td></td>
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<tr>
<td>No</td>
<td>1916</td>
<td>1812</td>
<td>0.10</td>
<td>0.32</td>
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<td>Yes</td>
<td>2271</td>
<td>2400</td>
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<tr>
<td>Prior hospitalization for heart failure</td>
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<td>No</td>
<td>1580</td>
<td>1545</td>
<td>0.10</td>
<td>0.19</td>
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<td>Yes</td>
<td>2607</td>
<td>2667</td>
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<td>Time since diagnosis of heart failure</td>
<td></td>
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<tr>
<td>≤1 yr</td>
<td>1275</td>
<td>1248</td>
<td>0.27</td>
<td>0.21</td>
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<tr>
<td>&gt;1 to 5 yr</td>
<td>1621</td>
<td>1611</td>
<td></td>
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</tr>
<tr>
<td>&gt;5 yr</td>
<td>1291</td>
<td>1353</td>
<td></td>
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</tbody>
</table>

Table 2. 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>
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<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>

* Hazard ratios were calculated with the use of stratified Cox proportional-hazard models. P values are two-sided and were calculated by means of a stratified log-rank test without adjustment for multiple comparisons.
† Scores on the Kansas City Cardiomyopathy Questionnaire (KCCQ) range from 0 to 100, with higher scores indicating fewer symptoms and physical limitations associated with heart failure. The treatment effect is shown as the least-squares mean (±SE) of the between-group difference.
‡ A total of 2670 patients in the LCZ696 group and 2638 patients in the enalapril group who did not have atrial fibrillation at the randomization visit were evaluated for new-onset atrial fibrillation during the study.
§ A decline in renal function was defined as end-stage renal disease or a decrease of 50% or more in the estimated glomerular filtration rate (eGFR) from the value at randomization or a decrease in the eGFR of more than 30 ml per minute per 1.73 m², to less than 60 ml per minute per 1.73 m².

### Table 3. Adverse Events during Randomized Treatment.*

<table>
<thead>
<tr>
<th>Event</th>
<th>LCZ696 (N = 4187) no. (%)</th>
<th>Enalapril (N = 4212) no. (%)</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>

* Shown are results of the analyses of prespecified safety events at any time after randomization. The numbers of patients who permanently discontinued a study drug were as follows: for hypotension, 36 (0.9%) in the LCZ696 group and 29 (0.7%) in the enalapril group (P = 0.38); for renal impairment, 29 (0.7%) and 59 (1.4%), respectively (P = 0.002); and for hyperkalemia, 11 (0.3%) and 15 (0.4%), respectively (P = 0.56).

† Angioedema was adjudicated in a blinded fashion by an expert committee.

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

Hazard ratio 0.60 (0.38-0.94)  
\(P = 0.027\)

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

Packer M et al. Circulation. 2015;131:54-61
Cumulative number of hospitalizations for heart failure in the enalapril and LCZ696 groups per 100 patients.

Rate ratio 0.77 (0.67-0.89)
P < 0.001

Packer M et al. Circulation. 2015;131:54-61
Mechanism of action: LCZ-696

LESSON #4: the PARADIGM HF clinical trial results are robust and merit strong consideration for clinical use; pay attention to the differential effect of LCZ-696 on NT-proBNP and BNP
Pharmacologic Treatment for Stage C HFrEF

HFrEF Stage C
NYHA Class I – IV

Treatment:

For NYHA class II-IV patients. Provided estimated creatinine >30 mL/min and K+ <5.0 mEq/dL

- **Class I, LOE A**
  - ACEI or ARB AND Beta Blocker

- For all volume overload, NYHA class II-IV patients
  - **Add**
  - **Class I, LOE C**
    - Loop Diuretics

- For persistently symptomatic African Americans, NYHA class III-IV
  - **Add**
  - **Class I, LOE A**
    - Hydral-Nitrates

- For NYHA class II-IV patients. Provided estimated creatinine >30 mL/min and K+ <5.0 mEq/dL
  - **Add**
  - **Class I, LOE A**
    - Aldosterone Antagonist

**ARNI**
Drugs That Reduce Mortality in Heart Failure With Reduced Ejection Fraction

Drugs that inhibit the renin-angiotensin system have modest effects on survival.

Based on results of SOLVD-Treatment, CHARM-Alternative, COPERNICUS, MERIT-HF, CIBIS II, RALES and EMPHASIS-HF & A - HeFT

Modified from M. Packer
Angiotensin Neprilysin Inhibition With LCZ696 Doubles Effect on Cardiovascular Death of Current Inhibitors of the Renin-Angiotensin System

Effect of ARB vs placebo derived from CHARM-Alternative trial
Effect of ACE inhibitor vs placebo derived from SOLVD-Treatment trial
Effect of LCZ696 vs ACE inhibitor derived from PARADIGM-HF trial
# Evidence-Based HFrEF Therapies

<table>
<thead>
<tr>
<th>Guideline Recommended Therapy</th>
<th>Relative Risk Reduction in Mortality</th>
<th>Number Needed to Treat for Mortality (standardized to 36 months)</th>
<th>NNT for Mortality</th>
<th>Relative Risk Reduction in HF Hospitalizations</th>
</tr>
</thead>
<tbody>
<tr>
<td>ACEI/ARB</td>
<td>17%</td>
<td>22 over 42 months</td>
<td>26</td>
<td>31%</td>
</tr>
<tr>
<td>ARNI</td>
<td>16%</td>
<td>36 over 27 months</td>
<td>27</td>
<td>21%</td>
</tr>
<tr>
<td>Beta-blocker</td>
<td>34%</td>
<td>28 over 12 months</td>
<td>9</td>
<td>41%</td>
</tr>
<tr>
<td>Aldosterone Antagonist</td>
<td>30%</td>
<td>9 over 24 months</td>
<td>6</td>
<td>35%</td>
</tr>
<tr>
<td>Hydralazine/Nitrate</td>
<td>43%</td>
<td>25 over 10 months</td>
<td>7</td>
<td>33%</td>
</tr>
<tr>
<td>CRT</td>
<td>36%</td>
<td>12 over 24 months</td>
<td>8</td>
<td>52%</td>
</tr>
<tr>
<td>ICD</td>
<td>23%</td>
<td>14 over 60 months</td>
<td>23</td>
<td>NA</td>
</tr>
</tbody>
</table>

We recommend that in patients with mild to moderate HF, an EF < 40%, an elevated HF level, or hospitalization for HF in the past 12 months, a serum potassium < 5.2 mmol/L and an eGFR ≥ 30 mL/min and treated with appropriate doses of guideline-directed medical therapy should be treated with LCZ696 in place of an ACE inhibitor or an angiotensin receptor blocker, with close surveillance of serum potassium and creatinine (Conditional Recommendation, High-Quality Evidence).

We suggest that in individuals with HFpEF, an elevated natriuretic peptide level, serum potassium < 5.0 mmol/L and an eGFR ≥30 ml/min, a mineralocorticoid receptor antagonist like spironolactone should be considered, with close surveillance of serum potassium and creatinine. (Weak Recommendation, Low Quality of Evidence).

We suggest that for patients with documented iron deficiency, oral or intravenous iron supplement be initiated to improve functional capacity (Weak Recommendation, Low-Quality Evidence).
Where are the gaps in information for LCZ-696?

- < 1,000 patients studied in the US
- Limited data in those with moderately severe or severe HF
- Premature study termination- overstates benefit and underestimates harm
- Open label run-in period- eliminates adverse drug reactions
- Negligible number of African Americans
- Long term safety data?
- **Costs: ~ $400/mo vs $4/mo (ACE-I)**
LESSON #5: Exercise more deliberation RE: initiation of LCZ 696 in those for whom we have less data: 1) advanced HF; 2) the elderly; 3) African Americans?; 4) those without a drug benefit plan
LATEST UPDATES ON LCZ 696
The newest data: TITRATION Trial

ESC HF, May 2015, LBCTs; Senni et al for the PARADIGM HF investigators

• TITRATION was a randomised, double blind study that assessed the safety and tolerability of initiating and up-titrating LCZ696 from 50mg BID to a target dose of 200mg BID in a 3-week (condensed) versus 6-week (conservative) regimen in patients with HFrEF (ejection fraction ≤35%).

• Primary endpoints were the proportion of patients experiencing pre-specified adverse events: symptomatic hypotension, hyperkalaemia, renal dysfunction, angioedema

• 540 patients enrolled; 498 randomized (92%); 86% completed the study

• Condensed arm - 78% success

• Conservative arm – 84% success

• Study participants included inpatients and ACE-I naïve patients
Drug Formulation

• Starting dose:
  • Sacubitril/valsartan: 49/51 mg
  • Sacubitril/Valsartan: 24/26 mg (for reduced GFR, < 30 ml/min)

• Target dose:
  • Sacubitril/Valsartan: 97/103 mg*

• Titration schedule:

• Q 2-4 weeks

*103 mg = 160 mg due to different pharmacokinetics for the valsartan salt in LCZ-696

Source: Prescriber’s Letter; August, 2015
Optional Networking Group:

**Purpose:** Connect directly with other hospitals to network and share best practice

**To Join:**
Look for question on November webinar registration link
Or
Contact Lynn/Shaina
Questions or Comments

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*For GWTG-HF information, we can direct you to your local QSI representative.
Please watch your email for a survey to provide us feedback on today’s webinar.
THANK YOU!