Heart Failure: Medical Treatment and Prevention

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Disclosure:

Mariell Jessup MD

• Speakers Bureau: NONE
• Advisory Board: NONE
• Honorarium: NONE

AHA Scientific Statement

Prevention of Heart Failure

Evolution of Heart Failure

<table>
<thead>
<tr>
<th>Risk Factors</th>
<th>Cellular Pathophysiology</th>
<th>Ventricular Remodeling</th>
<th>Ventricular Dysfunction</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aging</td>
<td>Hypertrophy</td>
<td>LVH</td>
<td>Systolic</td>
</tr>
<tr>
<td>Hypertension</td>
<td>Hyperplasia</td>
<td>Dilatation</td>
<td>Diastolic</td>
</tr>
<tr>
<td>Smoking</td>
<td>Inflammation</td>
<td>Both</td>
<td>Both</td>
</tr>
<tr>
<td>Dyslipidemia</td>
<td>Apoptosis</td>
<td>Both</td>
<td>Both</td>
</tr>
<tr>
<td>Diabetes</td>
<td>Fibrosis</td>
<td>Both</td>
<td>Both</td>
</tr>
<tr>
<td>Obesity</td>
<td>Structural Heart Disease</td>
<td>Both</td>
<td>Both</td>
</tr>
<tr>
<td>Toxicities</td>
<td>Without Symptoms</td>
<td>Both</td>
<td>Both</td>
</tr>
<tr>
<td>Genes</td>
<td>Symptomatic Heart Failure</td>
<td>Both</td>
<td>Both</td>
</tr>
</tbody>
</table>

Stage A
Stage B
Stage C
Stage D

AHA / ACC Stages of Heart Failure
In older persons with isolated systolic hypertension, stepped-care treatment based on low-dose chlorthalidone exerted a strong protective effect in preventing heart failure. Among patients with prior MI, an 80% risk reduction was observed.
Survival after HF diagnosis has improved over time, as shown by data from the Framingham Heart Study and the Olmsted County Study. However, the death rate remains high: ≈50% of people diagnosed with HF will die within 5 years.

Go et al. Heart Disease and Stroke Statistics—2014 Update
A Report From the American Heart Association
Pharmacologic Treatment for Stage C HF\(r\)EF

Acc/AHA 2013 HF Guidelines

Acute heart failure in all its manifestations and etiologies
Risk predictors and risk stratification

Biomarkers for diagnosis, triage, and guiding management

The NEW ENGLAND JOURNAL of MEDICINE

Angiotensin–Nepriyisin Inhibition versus Enalapril in Heart Failure

John J. McMurray, M.D., Milene Parker, M.D., Alhusayn Shehab, M.D., M.P.H., Jianjun Gong, Ph.D., Martin P. Safar, M.D., Abd R. Roda, Pharm.D., Joan I. Roskam, M.D., Victor C. Shi, M.D., Scott D. Solomon, M.D., Karl Sandberg, M.D., Ph.D., and Michael R. Zile, M.D., for the PARADIGM-HF Investigators and Committees
Neprilysin Inhibition Potentiates Actions of Endogenous Vasoactive Peptides to Balance Maladaptive Mechanisms in Heart Failure

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

Neprilysin inhibition

PARADIGM-HF

- Study description
  - Randomized, double-blind phase 3 trial
  - Evaluation of the efficacy and safety profile of angiotensin receptor-neprilysin inhibitor (ARNI) versus the ACE inhibitor, enalapril
  - 8442 patients with HFrEF (NYHA class II-IV)
  - Open-label run-in phase removed patients who were intolerant prior to randomization


PARADIGM-HF: Baseline Characteristics

<table>
<thead>
<tr>
<th></th>
<th>LCZ696 (n=4187)</th>
<th>Enalapril (n=4212)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>63.8 ± 11.5</td>
<td>63.8 ± 11.3</td>
</tr>
<tr>
<td>Women (%)</td>
<td>21.0%</td>
<td>22.6%</td>
</tr>
<tr>
<td>Ischemic cardiomyopathy (%)</td>
<td>59.9%</td>
<td>60.1%</td>
</tr>
<tr>
<td>LV ejection fraction (%)</td>
<td>29.6 ± 6.1</td>
<td>29.4 ± 6.3</td>
</tr>
<tr>
<td>NYHA functional class II / III (%)</td>
<td>71.8% / 23.1%</td>
<td>69.4% / 24.9%</td>
</tr>
<tr>
<td>Systolic blood pressure (mm Hg)</td>
<td>122 ± 15</td>
<td>121 ± 15</td>
</tr>
<tr>
<td>Heart rate (beats/min)</td>
<td>72 ± 12</td>
<td>73 ± 12</td>
</tr>
<tr>
<td>N-terminal pro-BNP (pg/ml)</td>
<td>1631 (885-3154)</td>
<td>1594 (886-3305)</td>
</tr>
<tr>
<td>B-type natriuretic peptide (pg/ml)</td>
<td>255 (155-474)</td>
<td>251 (153-465)</td>
</tr>
<tr>
<td>History of diabetes</td>
<td>35%</td>
<td>35%</td>
</tr>
<tr>
<td>Digitalis</td>
<td>29.3%</td>
<td>31.2%</td>
</tr>
<tr>
<td>Beta-adrenergic blockers</td>
<td>93.1%</td>
<td>92.9%</td>
</tr>
<tr>
<td>Mineralocorticoid antagonists</td>
<td>54.2%</td>
<td>57.0%</td>
</tr>
<tr>
<td>ICD and/or CRT</td>
<td>16.8%</td>
<td>16.3%</td>
</tr>
</tbody>
</table>

**PARADIGM-HF: Cardiovascular Death or Heart Failure Hospitalization (Primary Endpoint)**

![Graph depicting Kaplan-Meier estimates for Enalapril and LCZ696.](image)

- **Enalapril** (n=4212)
- **LCZ696** (n=4187)

**Kaplan-Meier Estimate of Cumulative Rates (%)**

- Days After Randomization: 360, 720, 1080, 180, 540, 900, 1260

**HR = 0.80 (0.73-0.87)**

**P = 0.000002**

**Number needed to treat = 21**

**PARADIGM-HF: Cardiovascular Death**

![Graph depicting Kaplan-Meier estimates for Enalapril and LCZ696.](image)

- **Enalapril** (n=4212)
- **LCZ696** (n=4187)

**Kaplan-Meier Estimate of Cumulative Rates (%)**

- Days After Randomization: 360, 720, 1080, 180, 540, 900, 1260

**HR = 0.80 (0.71-0.89)**

**P = 0.00004**

**Number needed to treat = 32**

**PARADIGM-HF: All-Cause Mortality**

![Graph depicting Kaplan-Meier estimates for Enalapril and LCZ696.](image)

- **Enalapril** (n=4212)
- **LCZ696** (n=4187)

**Kaplan-Meier Estimate of Cumulative Rates (%)**

- Days After Randomization: 360, 720, 1080, 180, 540, 900, 1260

**HR = 0.84 (0.76-0.93)**

**P < 0.0001**

PARADIGM-HF: Adverse Events

<table>
<thead>
<tr>
<th></th>
<th>LCZ696 (n=4187)</th>
<th>Enalapril (n=4212)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Prospectively identified adverse events</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Symptomatic hypotension</td>
<td>588</td>
<td>389</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Serum potassium &gt; 6.0 mmol/l</td>
<td>181</td>
<td>236</td>
<td>0.007</td>
</tr>
<tr>
<td>Serum creatinine ≥ 2.5 mg/dl</td>
<td>139</td>
<td>188</td>
<td>0.007</td>
</tr>
<tr>
<td>Cough</td>
<td>474</td>
<td>601</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Discontinuation for adverse event</td>
<td>449</td>
<td>516</td>
<td>0.02</td>
</tr>
<tr>
<td>Discontinuation for hypotension</td>
<td>36</td>
<td>29</td>
<td>NS</td>
</tr>
<tr>
<td>Discontinuation for hyperkalemia</td>
<td>11</td>
<td>15</td>
<td>NS</td>
</tr>
<tr>
<td>Discontinuation for renal impairment</td>
<td>29</td>
<td>59</td>
<td>0.001</td>
</tr>
<tr>
<td>Angioedema (adjudicated)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Medications, no hospitalization</td>
<td>16</td>
<td>9</td>
<td>NS</td>
</tr>
<tr>
<td>Hospitalized; no airway compromise</td>
<td>3</td>
<td>1</td>
<td>NS</td>
</tr>
<tr>
<td>Airway compromise</td>
<td>0</td>
<td>0</td>
<td></td>
</tr>
</tbody>
</table>


Conclusions - PARADIGM-HF

*In heart failure with reduced ejection fraction:*

**LCZ696 as compared to enalapril**
- Reduced the risk of CV death and HF hospitalization
- Reduced the risk of CV death by incremental 20%
- Reduced the risk of HF hospitalization by incremental 21%
- Reduced all-cause mortality by incremental 16%
- Incrementally improved symptoms and physical limitations

**LCZ696 as compared to enalapril**
- Less likely to cause cough, hyperkalemia or renal impairment
- Less likely to be discontinued due to an adverse event
- More hypotension, but no increase in discontinuations
- Not more likely to cause serious angioedema

A new drug class, capitalizing on an alternative pathway, combining the salutary effects of angiotensin inhibition and vasoactive peptide promotion.
Beneficial effects of long-term intravenous iron therapy with ferric carboymaltose in patients with symptomatic heart failure and iron deficiency

Piotr Ponikowski1,2, Dirk J. van Veldhuisen3, Josep Comin-Colet4, Georg Erst1,4, Michel Komajda1, Viacheslav Marsov4, Theresa McDonagh1, Alexander Parkhomenko1, Luigi Tavazzi1, Victoria Leosque1, Claudio Mor1, Bernard Roubert1, Gerasimos Filipatos1, Frank Ruschitzka1, and Stefan D. Anker1, for the CONFIRM-HF Investigators

CONFIRM-HF Design

• Multi-center, double-blind, placebo-controlled trial of 304 ambulatory symptomatic HF patients with left ventricular ejection fraction ≤45%, elevated natriuretic peptides, and iron deficiency (ferritin < 100 ng/mL or 100–300 ng/mL if transferrin saturation < 20%)
• Randomized 1 : 1 to i.v. iron, as ferric carboymaltose or placebo for 52 weeks.
• Primary end-point change in 6-min-walk-test (6MWT) distance from baseline to Week 24. Secondary end-points included changes in NYHA class, Patient Global Assessment (PGA), 6MWT distance, health related QoL, Fatigue Score and rate of hospitalization for worsening HF.

6-Min Walk Test and Fatigue over Time

Piotr Ponikowski et al. Eur Heart J 2015;36:657-668
Conclusions – CONFIRM HF

Treatment of symptomatic, iron-deficient HF patients with FCM over a 1-year period resulted in sustainable improvement in functional capacity, symptoms, and QoL and may be associated with risk reduction of hospitalization for worsening HF.
Ivabradine and outcomes in chronic heart failure (SHIFT): a randomised placebo-controlled study

Mechanism of Action

*Ivabradine* selectively inhibits the sinus node I(f) pacemaking current, thereby decreasing myocardial oxygen demand without effecting inotropy or blood pressure.
Inclusion Criteria: the SHIFT trial

- >18 years
- Class II to IV NYHA heart failure
- Ischaemic/non-ischaemic aetiology
- LV systolic dysfunction (EF <35%)
- Heart rate >70 bpm
- Sinus rhythm
- Documented hospital admission for worsening heart failure <12 months
SHIFT Primary Composite Endpoint
(CV death or hospital admission for worsening HF)

Cumulative frequency (%)

HR = 0.82 (0.75–0.90)
P < 0.0001

Placebo 18%
Ivabradine


Hospitalization for Heart Failure

Cumulative frequency (%)

HR = 0.74 (0.66–0.83)
P < 0.0001

Placebo 26%
Ivabradine


Death from heart failure

Cumulative frequency (%)

HR = 0.74 (0.58–0.94)
P = 0.014

Placebo 26%
Ivabradine

**Effect of ivabradine on outcomes**

<table>
<thead>
<tr>
<th>Endpoints</th>
<th>Hazard ratio</th>
<th>95% CI</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Primary composite endpoint (CV death or hospital admission for worsening HF)</td>
<td>0.82</td>
<td>[0.75;0.89]</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>All-cause mortality</td>
<td>0.90</td>
<td>[0.83;1.02]</td>
<td>0.092</td>
</tr>
<tr>
<td>Death from heart failure</td>
<td>0.74</td>
<td>[0.68;0.81]</td>
<td>&lt;0.014</td>
</tr>
<tr>
<td>All-cause hospital admission</td>
<td>0.89</td>
<td>[0.82;0.96]</td>
<td>&lt;0.003</td>
</tr>
<tr>
<td>Any CV hospital admission</td>
<td>0.85</td>
<td>[0.78;0.92]</td>
<td>0.0002</td>
</tr>
<tr>
<td>CV death/hospital admission for HF or non-fatal MI</td>
<td>0.82</td>
<td>[0.74;0.89]</td>
<td>0.0001</td>
</tr>
</tbody>
</table>


**Effect of ivabradine in prespecified subgroups**

- Age <65 years vs ≥65 years
- Sex Male vs Female
- Beta-blockers Yes vs No
- Aetiology of heart failure Non-ischaemic vs Ischaemic
- NYHA class II vs III or IV
- Diabetes Yes vs No
- Hypertension Yes vs No
- Baseline heart rate <77 bpm vs ≥77 bpm

**Mean heart rate reduction**

70% of patients on ivabradine 7.5 mg bid

Incidence of selected adverse events (n = 6492)

<table>
<thead>
<tr>
<th>Patients with an event</th>
<th>Ivabradine N=3232, n (%)</th>
<th>Placebo N=3260, n (%)</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>All serious adverse events</td>
<td>1450 (45%)</td>
<td>1553 (48%)</td>
<td>0.025</td>
</tr>
<tr>
<td>All adverse events</td>
<td>2439 (75%)</td>
<td>2423 (74%)</td>
<td>0.303</td>
</tr>
<tr>
<td>Symptomatic bradycardia</td>
<td>150 (5%)</td>
<td>32 (1%)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Asymptomatic bradycardia</td>
<td>184 (6%)</td>
<td>48 (1%)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Atrial fibrillation</td>
<td>306 (9%)</td>
<td>251 (8%)</td>
<td>0.012</td>
</tr>
<tr>
<td>Phosphenes</td>
<td>89 (3%)</td>
<td>17 (&lt;1%)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Blurred vision</td>
<td>17 (1%)</td>
<td>7 (&lt;1%)</td>
<td>0.042</td>
</tr>
</tbody>
</table>


Ivabradine significantly reduces major risks associated with heart failure:
- 18% reduction in CV death or hospital admission for worsening HF
- 26% reduction in death from heart failure
- 26% reduction in hospital admission for worsening heart failure

Benefits are apparent early, are consistent in predefined subgroups, and have been demonstrated on top of recommended therapy. Treatment is well tolerated.

Conclusion: the SHIFT trial

“Success consists of going from failure to failure without loss of enthusiasm.”

Winston Churchill
Thank You