What’s New in Heart Failure

14th Annual Contemporary Therapeutic Issues in Cardiovascular Disease
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What’s New in Heart Failure?

Aldosterone Antagonists
Aldosterone Antagonists: Guidelines

- **CCS**
  - Consider for patients with severe symptomatic chronic HF despite optimization of treatment and LVEF<30%
    - Benefit was mortality
  - Consider in AHF with LVEF less than 30% following acute MI

- **ACC/AHA/HFSA**
  - Moderately severe to severe symptoms and reduced LV dysfunction who can be carefully monitored for renal function and potassium
Eplerenone in Patients with Systolic Heart Failure and Mild Symptoms

EMPHASIS-HF*

Faiez Zannad, M.D., Ph.D., John J.V. McMurray, M.D., Henry Krum, M.B., PhD., Dirk J. van Veldhuisen, M.D., Ph.D., Karl Swedberg, M.D., Ph.D., Harry Shi, M.S., John Vincent, M.B., Ph.D., Stuart J Pocock, Ph.D. and Bertram Pitt, M.D. for the EMPHASIS-HF Study Group

ClinicalTrials.gov, NCT00232180

* Eplerenone in Mild Patients Hospitalization And Survival Study in Heart Failure
Disposition of Patients

EMPHASIS-HF Investigators (29 countries, 278 sites)

2737 Randomized

1364 Randomized to eplerenone 25-50 mg/d
- 4 did not start study drug
- 17 lost to follow up

1373 Randomized to placebo
- 4 did not start study drug
- 15 lost to follow up

Median follow-up time 21 months, 4783 patient-years of follow-up
Primary Endpoint Cardiovascular Death or Hospitalization for HF

HR [95% CI] = 0.63 [0.54, 0.74] P < 0.0001

Placebo
356 (25.9)

Eplerenone
249 (18.3)

No. at Risk
Placebo 1373 848 512 199
Eplerenone 1364 925 562 232

*Unadjusted HR 0.66; 0.56, 0.78; p<0.0001
Mortality From Any Cause

HR [95% CI] = 0.76 [0.62, 0.93] P = 0.0081

All-Cause Mortality, Cumulative K-M Rate (%)

No. at Risk
Placebo 1373
Eplerenone 1364

Years from Randomization
0 1 2 3
Placebo 213 (15.5)
Eplerenone 171 (12.5)

*Unadjusted HR, 0.78; 0.64, 0.95; p=0.01
ALDOSTERONE ANTAGONISTS

- Spironolactone
- Eplerenone (Inspra®)
Eplerenone – What is it?

- Selective aldosterone receptor antagonist (SARA)
  - Minimal effects at other steroid receptors
  - Limits progestational and antiandrogenic side effects:
    - Gynecomastia
    - Impotence
    - Menstrual irregularities
    - Hirsutism
Other Important Differences

- **Half Life**
  - Shorter – 4-6h vs ~2-16h (active metabolites)

- **Metabolism**
  - Inactive metabolites
  - 3A4 involved → *drug interactions*

- **Cost**
  - ~$2.60/tab
  - Exceptional Access in Ontario
Drug Interactions

- Contraindicated:
  - Potassium-sparing diuretics
  - K+ supplements
  - Strong CYP 3A4 inhibitors:
    - Ketoconazole, Itraconazole
    - Nefazodone
    - Clarithromycin, Telithromycin
    - Ritonavir, Nelfinavir
Drug Interactions

- **Mild-to-moderate inhibitors**: “dose should not exceed 25mg”
  - Amiodarone
  - Verapamil, Diltiazem
  - Erythromycin, Fluconazole
  - Saquinavir

- **Potent CYP-3A4 inducers**: “not recommended”
  - Carbamazepine, Phenytoin, Phenobarb
  - Rifampin
  - St. John’s Wort
What’s New in Heart Failure?

Heart Rate Reduction?
Heart Rate Lowering Therapy

- Raised resting HR predicts CV events\(^1\),\(^2\)
  - HF hospitalizations
- Beta blockers continue to be underused or underdosed
  - Some patients have persistently high resting HR despite beta blocker therapy
- Other means of lowering resting HR?

\(^1\)Diaz A Eur H Journal 2005;26, \(^2\)Fox K Lancet 2008;372
Systolic Heart failure treatment with the If inhibitor ivabradine Trial
Study Design

Ivabradine 5 mg bid

Matching placebo, bid

Ivabradine 7.5/5/2.5 mg bid according to HR and tolerability

Every 4 months

Screening 7 to 30 days

D0 D14 D28 M4

3.5 years

## Baseline Characteristics

<table>
<thead>
<tr>
<th></th>
<th>Ivabradine</th>
<th>Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Count</strong></td>
<td>3241</td>
<td>3264</td>
</tr>
<tr>
<td><strong>Mean age, y</strong></td>
<td>60.7</td>
<td>60.1</td>
</tr>
<tr>
<td><strong>Male, %</strong></td>
<td>76</td>
<td>77</td>
</tr>
<tr>
<td><strong>Ischaemic aetiology, %</strong></td>
<td>68</td>
<td>67</td>
</tr>
<tr>
<td><strong>NYHA II, %</strong></td>
<td>49</td>
<td>49</td>
</tr>
<tr>
<td><strong>NYHA III/IV, %</strong></td>
<td>51</td>
<td>51</td>
</tr>
<tr>
<td><strong>Previous MI, %</strong></td>
<td>56</td>
<td>56</td>
</tr>
<tr>
<td><strong>Diabetes, %</strong></td>
<td>30</td>
<td>31</td>
</tr>
<tr>
<td><strong>Hypertension, %</strong></td>
<td>67</td>
<td>66</td>
</tr>
</tbody>
</table>

## Baseline Characteristics

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<tbody>
<tr>
<td></td>
<td>3241</td>
<td>3264</td>
</tr>
<tr>
<td>Mean heart rate, bpm</td>
<td>80</td>
<td>80</td>
</tr>
<tr>
<td>Mean LVEF, %</td>
<td>29</td>
<td>29</td>
</tr>
<tr>
<td>Mean SBP, mm Hg</td>
<td>122</td>
<td>121</td>
</tr>
<tr>
<td>Mean DBP, mm Hg</td>
<td>76</td>
<td>76</td>
</tr>
<tr>
<td>eGFR, mL/min/1.73 m²</td>
<td>75</td>
<td>75</td>
</tr>
</tbody>
</table>

Background Beta-blocker Treatment

Patients (%)

- **BB at randomization**
  - Ivabradine: 89%
  - Placebo: 89%

- **At least 50% target daily dose**
  - Ivabradine: 56%
  - Placebo: 56%

- **Target daily dose**
  - Ivabradine: 26%
  - Placebo: 26%

Primary Composite Endpoint

(CV death or hospital admission for worsening HF)

Cumulative frequency (%)

HR = 0.82 (0.75–0.90)

Placebo

Ivabradine

Death from Heart Failure

HR = 0.74 (0.58–0.94)
P = 0.014

## 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;0.90]</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>All-cause mortality</td>
<td>0.90</td>
<td>[0.80;1.02]</td>
<td>0.092</td>
</tr>
<tr>
<td>Death from heart failure</td>
<td>0.74</td>
<td>[0.58;0.94]</td>
<td>0.014</td>
</tr>
<tr>
<td>All-cause hospital admission</td>
<td>0.89</td>
<td>[0.82;0.96]</td>
<td>0.003</td>
</tr>
<tr>
<td>Any CV hospital admission</td>
<td>0.85</td>
<td>[0.78;0.92]</td>
<td>&lt;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>&lt;0.0001</td>
</tr>
</tbody>
</table>

Incidence of Selected Adverse Events (n = 6492)

<table>
<thead>
<tr>
<th>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><strong>1450</strong> (45%)</td>
<td><strong>1553</strong> (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 (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>

What’s New in Heart Failure?

Diuretic Therapy
Diuretic Optimization Strategies Evaluation in Acute Heart Failure (DOSE)

G. Michael Felker, MD, MHS, FACC
Christopher M. O’Connor, MD, FACC

on behalf of the

NHLBI Heart Failure Clinical Research Network
Study Design

Acute Heart Failure (1 symptom AND 1 sign)
Home diuretics dose $\geq 80$ mg and $\leq 240$ mg furosemide
$<24$ hours after admission

$2 \times 2$ factorial randomization

High Dose (2.5x oral)
Continuous infusion

High Dose (2.5x oral)
Q12 IV bolus

Low Dose (1x oral)
Continuous infusion

Low Dose (1x oral)
Q12 IV bolus

48 hours

1) Change to oral
2) continue current dose
3) 50% increase in dose

72 hours

Co-Primary endpoints:
Change in creatinine from baseline to 72 hours
Patient Global Assessment VAS area under curve over 72 hours
Inclusion Criteria

• ≥18 years old, within 24h of admission
• Prior clinical diagnosis of heart failure with daily home use of oral loop diuretic for at least one month
• Daily oral dose of furosemide ≥ 80 mg and ≤240 mg (or equivalent)
• Heart failure defined by at least 1 symptom (dyspnea, orthopnea, or edema) AND 1 sign (rales on auscultation, peripheral edema, ascites, pulmonary vascular congestion on chest radiography)
• Anticipated need for IV loop diuretics for at least 48 hours
Exclusion Criteria

- Received or planned IV vasoactive treatment (inotropes, vasodilators) or ultra-filtration therapy for heart failure
- Systolic BP <90 mmHg
- Serum creatinine >3.0 mg/dl at baseline or renal replacement therapy
- Acute coronary syndrome within 4 weeks
- Anticipated need for coronary angiography or other procedures requiring IV contrast
Patients

- 66y, 73% male, 72% caucasian, 50% DM
- Furosemide baseline ~130mg/day
- 74% CHF hospitalization in last 12 months
- EF~35%
- Mean SBP: 119
- Mean Cr: ~140umol/L
- Median time to randomization: 14h
Results: Primary Endpoint

• No difference in PGA VAS
  – P=0.47 for CI vs Q12H
  – P=0.06 for HD vs LD

• Change in Creatinine?
Change in Creatinine at 72 hours

<table>
<thead>
<tr>
<th></th>
<th>Low</th>
<th>High</th>
</tr>
</thead>
<tbody>
<tr>
<td>Q12 Continuous</td>
<td>0.05</td>
<td>0.07</td>
</tr>
<tr>
<td></td>
<td>p = 0.45</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Low</td>
<td>0.04</td>
<td>0.08</td>
</tr>
<tr>
<td></td>
<td>p = 0.21</td>
<td></td>
</tr>
</tbody>
</table>
Proportion with Worsening Renal Function: High vs. Low

% with Δ Cr > 27 umol/L

Time (days)

Low
High
Death, Rehospitalization, or ED Visit

HR for Continuous vs. Q12 = 1.19
95% CI 0.86, 1.66, p = 0.30

HR for High vs. Low = 0.83
95% CI 0.60, 1.16, p = 0.28
## Secondary Endpoints: Low vs. High Intensification

<table>
<thead>
<tr>
<th>Endpoint</th>
<th>Low</th>
<th>High</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dyspnea VAS AUC at 72 hours</td>
<td>4478</td>
<td>4668</td>
<td>0.041</td>
</tr>
<tr>
<td>% free from congestion at 72 hrs</td>
<td>11%</td>
<td>18%</td>
<td>0.091</td>
</tr>
<tr>
<td>Change in weight at 72 hrs</td>
<td>-5.3 lbs</td>
<td>-8.2 lbs</td>
<td>0.011</td>
</tr>
<tr>
<td>Net volume loss at 72 hrs</td>
<td>3575 mL</td>
<td>4899 mL</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>% Treatment failure</td>
<td>37%</td>
<td>40%</td>
<td>0.56</td>
</tr>
<tr>
<td>% with Cr increase &gt; 25umol/L at 72 hrs</td>
<td>14%</td>
<td>23%</td>
<td>0.041</td>
</tr>
<tr>
<td>Length of stay, days (median)</td>
<td>6</td>
<td>5</td>
<td>0.55</td>
</tr>
</tbody>
</table>
Conclusions

• There was no statistically significant difference in global symptom relief or change in renal function at 72 hours for either:
  – Intermittent bolus vs. continuous infusion
  – Low intensification vs. high intensification