Beyond ACE-inhibitors for Heart Failure

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NCVH Birmingham 2015
Current Therapy HFrEF

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.
Entresto = ARNI
**Neprilysin**

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

- Neurohormonal activation
- Vascular tone
- Cardiac fibrosis, hypertrophy
- Sodium retention

**Inactive metabolites**
PARADIGM-HF

NYHA class II-IV heart failure

LV ejection fraction ≤ 40% ➔ 35%

BNP ≥ 150 (or NT-proBNP ≥ 600), lower if hospitalized within 12 months

Any use of ACE inhibitor or ARB

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
10,521 patients screened at 1043 centers in 47 countries

Did not fulfill criteria for randomization (n=2079)

Randomized erroneously or at sites closed due to GCP violations (n=43)

8399 patients randomized for ITT analysis

**ARNI** (n=4187)
- At last visit
  - 375 mg daily
  - 11 lost to follow-up

**Enalapril** (n=4212)
- At last visit
  - 18.9 mg daily
  - 9 lost to follow-up

median 27 months of follow-up
CV Death/HF Admission

Kaplan-Meier Estimate of Cumulative Rates (%)

Enalapril
(n=4212)

ARNI
(n=4187)

Days After Randomization

Patients at Risk

<table>
<thead>
<tr>
<th></th>
<th>LCZ696</th>
<th>Enalapril</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>4187</td>
<td>4212</td>
</tr>
<tr>
<td>180</td>
<td>3922</td>
<td>3883</td>
</tr>
<tr>
<td>360</td>
<td>3663</td>
<td>3579</td>
</tr>
<tr>
<td>540</td>
<td>3018</td>
<td>2922</td>
</tr>
<tr>
<td>720</td>
<td>2257</td>
<td>2123</td>
</tr>
<tr>
<td>900</td>
<td>1544</td>
<td>1488</td>
</tr>
<tr>
<td>1080</td>
<td>896</td>
<td>853</td>
</tr>
<tr>
<td>1260</td>
<td>249</td>
<td>236</td>
</tr>
</tbody>
</table>

HR = 0.80 (0.73-0.87)
P = 0.0000002
Number needed to treat = 21
CV Death

HR = 0.80 (0.71-0.89)
P = 0.00004
Number need to treat = 32
# Adverse Events

<table>
<thead>
<tr>
<th></th>
<th>ARNI (n=4187)</th>
<th>Enalapril (n=4212)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Prospectively identified adverse events</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Symptomatic hypotension</td>
<td>588</td>
<td>388</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><strong>Discontinuation for adverse event</strong></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><strong>Angioedema (adjudicated)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>19</td>
<td>10</td>
<td>NS</td>
</tr>
</tbody>
</table>
PARADIGM HF

ARNI *more effective*...

- 20% reduction in CV death
- 21% reduction in hospitalization

...and *better tolerated* than Enalapril

Less cough, hyperkalemia, renal failure
No significant increase in angioedema
ARNI (Entresto)

Approved to reduce hospitalizations/death in patients with chronic HF (NYHAII-IV) and reduced EF

Avoid in:
- ACE inhibitors
- Pregnancy
- SBP<90
- Hx angioedema
- Aliskiren + DM
ARNI (Entresto) Dosing

ACE
- >10mg Lis/Enal
  >5mg Ramipril
  Start ARNI 49/51mg BID
- <10mg Lis/Enal
  <5mg Ramipril
  Start ARNI 24/26mg BID

ARB
- >160 Val, >50 Losa, >10 Olm
  Start ARNI 49/51mg BID
- <160 Val, <50 Losa, <10 Olm
  Start ARNI 24/26mg BID

Neither
- Start ARNI 24/26mg BID

36hr washout

Double dose q2-4wks to target 97/103mg BID

* Use reduced dose in GFR <30, mod hepatic impairment
Where are we now?

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
- Elevated heart rate is associated with poor outcomes in heart failure
- Heart rate remains elevated in many heart failure patients despite treatment
- Ivabradine is a novel heart rate-lowering agent in the sino-atrial node
CV Death or Hospitalization

Hazard ratio = 0.76

P < 0.0001

Patients with primary composite end point (%)

Time (months)

Placebo

Ivabradine
Reduction in Hospitalizations

Hazard ratio = 0.83

\[ P = 0.0166 \]

Patients with cardiovascular death (%)

<table>
<thead>
<tr>
<th>Time (months)</th>
<th>Placebo</th>
<th>Ivabradine</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td></td>
<td></td>
</tr>
<tr>
<td>6</td>
<td></td>
<td></td>
</tr>
<tr>
<td>12</td>
<td></td>
<td></td>
</tr>
<tr>
<td>18</td>
<td></td>
<td></td>
</tr>
<tr>
<td>24</td>
<td></td>
<td></td>
</tr>
<tr>
<td>30</td>
<td></td>
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</tbody>
</table>

\[ \text{Patients with cardiovascular death (%) at each time point.} \]
Reduction in CV Death

Hazard ratio = 0.91
P = 0.128

Patients with cardiovascular death (%)
Effect According to HR

Patients with primary composite end point (%)

## Side Effects

<table>
<thead>
<tr>
<th>Side Effect</th>
<th>Ivabradine (N=3,260)</th>
<th>Placebo (N=3,278)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bradycardia</td>
<td>10%</td>
<td>2.2%</td>
</tr>
<tr>
<td>Atrial Fibrillation</td>
<td>8.3%</td>
<td>6.6%</td>
</tr>
<tr>
<td>Phosphenes, visual brightness</td>
<td>2.8%</td>
<td>0.5%</td>
</tr>
<tr>
<td>Hypertension, blood pressure increase</td>
<td>8.9%</td>
<td>7.8%</td>
</tr>
</tbody>
</table>
## Dosing

### Recommended starting dose

<p>| | |</p>
<table>
<thead>
<tr>
<th></th>
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<tbody>
<tr>
<td>5mg tablet by mouth twice daily with meals</td>
<td>or</td>
</tr>
<tr>
<td>2.5mg tablet by mouth twice daily for patients in whom bradycardia could lead to hemodynamic compromise or with a history of conduction defects</td>
<td></td>
</tr>
</tbody>
</table>

### After 2 weeks, check resting heart rate

<table>
<thead>
<tr>
<th>Heart Rate</th>
<th>Action</th>
</tr>
</thead>
<tbody>
<tr>
<td>&gt;60 bpm</td>
<td>Increase dose by 2.5mg twice daily up to max of 7.5mg twice daily</td>
</tr>
<tr>
<td>50-60 bpm (target range)</td>
<td>Maintain dose</td>
</tr>
</tbody>
</table>
| <50 bpm | Decrease dose by 2.5mg twice daily  
*Discontinue therapy if current dose is 2.5mg twice daily |
Ivabradine (Corlanor)

Approved for *stable*, chronic HF (EF <35%) in sinus rhythm with resting HR >70.

**Avoid** in:
- ADHF
- Bradycardia
- Conduction disturbances
- Liver failure
- SBP<90
- Strong inhibitors of CYP3A4