Optimal pharmacological sequence of hormonal blockade in the treatment of HF.

Roberto Concepcion, MD, FACC
Chief of Cardiology Service DIPRECA Hospital. Assistant Professor of Internal Medicine and Cardiology. Universidad Diego Portales, Santiago de Chile.
Governor Chile Chapter of ACC
I have not a financial relationship to disclosure
Trend in HF

- Reduction in HF mortality (12%)

- Increase aging population

- Higher incidence of cardiac risk factors

- Higher prevalence of HF

Source: Framingham, Olmstec County, Canada (ICES)
At Risk for Heart Failure

**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
  - or 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

Heart Failure

**HFpEF**
- Refractory symptoms of HF at rest, despite GDMT

**HFrEF**
- Refractory symptoms of HF at rest, 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
Neurohormonal Activation and Rationale
For Standard Therapy for Systolic Heart Failure
Neurohormonal activation is a central mechanism of progressive HF

- Initially supports the circulation
- Ultimately highly negative impact
Decline In Systolic Function Leads To Activation Of Three Major Neurohormonal Systems

• Ang=angiotensin; AT1R=angiotensin II type 1 receptor; HF=heart failure; NPs=natriuretic peptides; NPRs=natriuretic peptide receptors; RAAS=renin-angiotensin-aldosterone system
  Kemp & Conte. Cardiovascular Pathology 2012;365–371;
Guideline-Directed Medical Therapy

Decrease in mortality (%)

- ACE inhibitor
- Angiotensin-receptor blocker
- Beta-blocker
- Mineralocorticoid-receptor blocker
Addition of β-Blockade to ACE Inhibition Reduces Mortality in Heart Failure

US Carvedilol Trials

Carvedilol (n=696)

Placebo (n=398)

Probability of Survival

Cumulative Mortality (%)

34% ↓
P=.0062 (adjusted)

MERIT-HF

Placebo (n=2,001)

Metoprolol CR/XL (n=1,990)

COPERNICUS

Carvedilol (n=1,156)

Bisoprolol (n=1,327)

CIBIS-II

Survival (%)

Survival (n=1,320)

P=.0014 (adjusted)


Neurohormonal blockade in HF

Angiotensinogen → Angiotensin I → Angiotensin II

Renin

ACE

AT1 Receptor stimulation

Aldosterone Release

Bradykinin

ACE Inhibitors

Inactive peptides → Reduced NO and vasodilating PGs

Angiotensin receptor blockers

Aldosterone Antagonists

Vasoconstriction, Na retention, myocyte hypertrophy and apoptosis, endothelial dysfunction, sympathetic activation, free radical generation, etc
Neurohormonal blockade in HF – revisited again

Active natriuretic peptides
Angiotensinogen → Renin → Angiotensin I → Angiotensin II → Angiotensin receptor blockers

Inactive natriuretic peptides
Neprilysin → LCZ696

AT1 Receptor stimulation → Aldosterone Release

Aldosterone Antagonists

ACE Inhibitors

Bradykinin

Reduced NO and vasodilating PGs
LCZ696
- A novel ARNI compound -

Complex with two active components:

- AHU377 pro-drug; further metabolized to the neprilysin inhibitor LBQ657

*Plus*

- Valsartan; angiotensin receptor (AT1) blocker
Now on to HF with reduced EF...

• The PARADIGM HF Study
  • Designed to assess whether the long-term effects of LCZ696 were superior to an ACEi in reducing morbidity and mortality

• Powered to detect difference in mortality
PARADIGM-HF: Study Design

**Single-blind active run-in period**
- Enalapril 10 mg BID*
- LCZ696 100 mg BID†
- LCZ696 200 mg BID‡

**Randomization**
n=8442

**Double-blind Treatment period**
- LCZ696 200 mg BID‡
- Enalapril 10 mg BID§

2 Weeks 1–2 Weeks 2–4 Weeks

Median of 27 months’ follow-up

On top of standard HFrEF therapy (excluding ACEIs and ARBs)

**Note:** Health Canada approved corresponding doses for LCZ696 are as follows:
- LCZ696 100 mg: 48.6 mg sacubitril / 51.4 mg valsartan
- LCZ696 200 mg: 97.2 mg sacubitril / 102.8 mg valsartan

- *Enalapril 5 mg BID (10 mg TDD) for 1–2 weeks followed by enalapril 10 mg BID (20 mg TDD) as an optional starting run-in dose for those patients who are treated with ARBs or with a low dose of ACEI; †200 mg TDD; ‡400 mg TDD; §20 mg TDD.
## Baseline Characteristics

<table>
<thead>
<tr>
<th>Characteristic</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, n (%)</td>
<td>879 (21.0)</td>
<td>953 (22.6)</td>
</tr>
<tr>
<td>Ischemic cardiomyopathy, n (%)</td>
<td>2506 (59.9)</td>
<td>2530 (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, n (%)</td>
<td></td>
<td></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>SBP, mmHg</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>NT pro-BNP, pg/mL (IQR)</td>
<td>1631 (885–3154)</td>
<td>1594 (886–3305)</td>
</tr>
<tr>
<td>BNP, pg/mL (IQR)</td>
<td>255 (155–474)</td>
<td>251 (153–465)</td>
</tr>
<tr>
<td>Treatments at randomization, n (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diuretics</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>ß-blockers</td>
<td>3899 (93.1)</td>
<td>3912 (92.9)</td>
</tr>
<tr>
<td>Mineralocorticoid antagonists</td>
<td>2271 (54.2)</td>
<td>2400 (57.0)</td>
</tr>
<tr>
<td>ICD</td>
<td>623 (14.9)</td>
<td>620 (14.7)</td>
</tr>
<tr>
<td>CRT</td>
<td>292 (7.0)</td>
<td>282 (6.7)</td>
</tr>
</tbody>
</table>
Primary endpoint:

Death from CV causes or first hospitalization for HF

Hazard ratio = 0.80 (95% CI: 0.73–0.87) p<0.001

NNT*=21 patients

Cumulative probability

No at risk

<table>
<thead>
<tr>
<th>LCZ696</th>
<th>4187</th>
<th>3922</th>
<th>3663</th>
<th>3018</th>
<th>2257</th>
<th>1544</th>
<th>896</th>
<th>249</th>
</tr>
</thead>
<tbody>
<tr>
<td>Enalapril</td>
<td>4212</td>
<td>3883</td>
<td>3579</td>
<td>2922</td>
<td>2123</td>
<td>1488</td>
<td>853</td>
<td>236</td>
</tr>
</tbody>
</table>
### Safety

<table>
<thead>
<tr>
<th>Event, n (%)</th>
<th>LCZ696 (n=4187)</th>
<th>Enalapril (n=4212)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Hypotension</strong></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 SBP &lt;90 mmHg</td>
<td>112 (2.7)</td>
<td>59 (1.4)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td><strong>Elevated serum creatinine</strong></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><strong>Elevated serum potassium</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&gt;5.5 mmol/L</td>
<td>674 (16.1)</td>
<td>727 (17.3)</td>
<td>0.15</td>
</tr>
<tr>
<td>&gt;6.0 mmol/L</td>
<td>181 (4.3)</td>
<td>236 (5.6)</td>
<td>0.007</td>
</tr>
<tr>
<td><strong>Cough</strong></td>
<td>474 (11.3)</td>
<td>601 (14.3)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td><strong>Angioedema</strong> (adjudicated by a blinded expert committee)</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>Catecholamines or glucocorticoids without hospitalization</td>
<td>6 (0.1)</td>
<td>4 (0.1)</td>
<td>0.52</td>
</tr>
<tr>
<td>Hospitalized 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>

Fewer patients in the LCZ696 group than in the enalapril group stopped their study medication because of an AE.
Sacubitril/Valsartan prevents disease progression

- Subanalysis of PARADIGM HF
  - Sacubitril/Valsartan reduced ED visits, hospitalization, inotrope use
  - Less intensification of HF therapy
  - Lower troponin and NT pro BNP levels
  - Improved symptom scores

Packer et al Circulation 2015
Too good to be true?

• Single trial
• Target doses may not be achievable in real world
• Low baseline use of ICD and CRT
  • May mitigate benefit with increase device use
• Higher incidence of hypotension vs. ACEi
• Not representative of patients with more advanced HF
• Enalapril dose?
Concerns

**COST: ISSUE IN LATIN AMERICA**
Yancy, CW, et al.
Heart Failure Focused Update on Pharmacological Therapy

2016 ACC/AHA/HFSA Focused Update on New Pharmacological Therapy for Heart Failure: An Update of the 2013 ACCF/AHA Guideline for the Management of Heart Failure

A Report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines and the Heart Failure Society of America

<p>| Recommendations for Renin-Angiotensin System Inhibition With ACE Inhibitor or ARB or ARNI |
|-----------------------------------------------|-------------------------------------------------|</p>
<table>
<thead>
<tr>
<th>COR</th>
<th>LOE</th>
<th>Recommendations</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>ACE: A</td>
<td>The clinical strategy of inhibition of the renin-angiotensin system with ACE inhibitors (Level of Evidence: A) (9-14), OR ARBs (Level of Evidence: A) (15-18), OR ARNI (Level of Evidence: B-R) (19) in conjunction with evidence-based beta blockers (20-22), and aldosterone antagonists in selected patients (23, 24), is recommended for patients with chronic HFrEF to reduce morbidity and mortality.</td>
</tr>
<tr>
<td>ARB: A</td>
<td></td>
<td></td>
</tr>
<tr>
<td>ARNI: B-R</td>
<td></td>
<td></td>
</tr>
<tr>
<td>III: Harm</td>
<td>B-R</td>
<td>ARNI should not be administered concomitantly with ACE inhibitors or within 36 hours of the last dose of an ACE inhibitor (31, 32).</td>
</tr>
<tr>
<td>III: Harm</td>
<td>C-EO</td>
<td>ARNI should not be administered to patients with a history of angioedema.</td>
</tr>
</tbody>
</table>