HEART FAILURE WITH REDUCED EJECTION FRACTION
STATE OF THE ART

Felix J. Rogers, DO, FACOI
April 29, 2018
Heart Failure Management

If your only tool is a hammer…

- Models of pharmacologic management
  - Volume overload
A Traditional Model for Chronic Heart Failure

- LV dysfunction
  - Cardiac output
  - Ventricular filling pressure

- Systemic vascular resistance and wall stress (afterload)
  - Ventricular filling pressure and blood volume (preload)

- Organ perfusion
  - Neurohumoral activation
A Clinical Model

From Mann, DL *Circulation* 1999; 100: 999-1008

Cardiorenal model
- Diuretics

Cardiocirculatory model
- Inotropes
- Vasodilators

Symptom relief

Neurohormonal model
- ACEI
- β-blocker

Prevention of disease progression
A Comprehensive Model
From Mann, DL *Circulation* 1999; 100: 999-1008
The New Paradigm, 2005

Electromechanical therapy
  • AICD

Restoration of myocardial function
  • Cardiac resynchronization therapy
  • Restoration of myocardial twist
  • Surgical approaches to remodeling

• Prevention of sudden death
Amiodarone vs AICD in HFpEF
CRT for HFrEF, CARE HF Study.
CARE – HF Trial of CRT vs medical therapy in HFrEF
New models for management of HF

- Pharmacologic
- Electromechanical
- Mechanical
- Systemic
New models for management of HF

• Pharmacologic
  • Sacubritil/Valsartan
  • Beta blocker, MRA
  • Diuretic

• Electromechanical
  • AICD
  • CRT + AICD

• Mechanical
  • LVAD
  • Transplant

• Systemic
  • Sleep apnea
  • Exercise
New models for management of HF

- Pharmacologic
  - Sacubritil/Valsartan
  - Beta blocker, MRA
  - Diuretic
  - Anticoagulation

- Electromechanical
  - AICD
  - CRT + AICD
  - Pulmonary vein isolation for atrial fibrillation

- Mechanical
  - LVAD

- Systemic interventions:
  - Detection of CAD, Anemia, Sleep apnea
Not covered today

• Ivradabine
• Valvular interventions
  • TAVR
  • MAVR
  • TAVR
• Coronary artery revascularization
• Heart failure with mid-range ejection fraction (HFmrEF)
Not covered today

- Ivradabine
- Valvular interventions
  - TAVR
  - MAVR
  - TAVR
- Coronary artery revascularization
- Heart failure with mid-range ejection fraction (HFmrEF)

Now, on to

Pharmacologic therapy
**Endogenous Compensatory Peptides**

NPs, Bradykinin, ADM

- **Vasodilation**
  - ▼ Blood pressure
  - ▼ Sympathetic tone
  - ▲ Natriuresis/diuresis
  - ▼ Vasopressin
  - ▼ Aldosterone
  - ▼ Fibrosis
  - ▼ Hypertrophy

**Effects of Sacubitril/valsartan in HFrEF**

**Neprilysin Inhibitor**

Sacubitril/valsartan

**Suppress deleterious effects of RAAS**

**Enhance the beneficial effects of endogenous compensatory peptides**

ENTRESTO®
Effects on Neprilysin and RAAS

Increases effects of endogenous compensatory peptides

- **↑** Vasodilation
- **↑** Natriuretic and diuretic effects
- **↓** Proliferation
- **↓** Hypertrophy
- **↓** SNS outflow/sympathetic tone
- **↓** Aldosterone secretion
- **↓** Detrimental effects of vascular remodeling

Suppressing RAAS-mediated effects

- **↓** Vasoconstriction
- **↓** Sodium and water retention
- **↓** Ventricular hypertrophy/remodeling
- **↓** Aldosterone secretion
- **↓** Cardiac fibrosis
- **↓** Sympathetic tone
- **↓** Systemic vascular resistance

cGMP = cyclic guanosine monophosphate; RAAS = renin-angiotensin-aldosterone system; SNS = sympathetic nervous system

PARADIGM-HF TRIAL
KEY FINDINGS
PARADIGM-HF

Study Design

Phase 3 Trial to Examine the Efficacy of Sacubitril/Valsartan vs Enalapril in Patients With HFrEF\textsuperscript{1,2}

N=8442 patients with chronic HF
(NYHA class II–IV with LVEF ≤40%) and elevated BNP

**Double-Blind Randomized Treatment Period**

**Randomization**

**Single-blind run-in period**

- **Enalapril**
  - 10 mg BID
  - 2 weeks
- **Sac/val**
  - 49/51 mg BID
  - 1–2 weeks
- **Sac/val**
  - 97/103 mg BID
  - 2–4 weeks

Testing tolerability to target doses of enalapril and sac/val

- **Enalapril 10 mg BID**
  - On top of standard HF therapy, excluding ACEIs and ARBs\textsuperscript{3}

- **Sac/val 97/103 mg BID**

A 36 hour washout was required after single blind enalapril run-in and also at end of entresto single blind run-in prior to being randomized

- **Primary outcome**: To demonstrate superiority of sacubitril/valsartan over enalapril in reducing composite of death from CV causes or a first hospitalization for HF

BID, twice daily; BNP, brain natriuretic peptide; NYHA, New York Heart Association.

\textsuperscript{a}Enalapril 5 mg BID for 1–2 weeks followed by enalapril 10 mg BID was an optional starting run-in dose for patients treated with ARBs or with a low dose of ACEI.

\textsuperscript{b}Dosing in clinical trials was based on the total amount of both components of sac/val; 24/26 mg, 49/51 mg, and 97/103 mg were referred to as 50 mg, 100 mg, and 200 mg, respectively. Sac/val was formerly known as LCZ696 in clinical trials.

# PARADIGM-HF

*Baseline Characteristics*

<table>
<thead>
<tr>
<th>Characteristic*</th>
<th>Sac/Val (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>Female, 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>LVEF (%)</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, mm Hg</td>
<td>122 ± 15</td>
<td>121 ± 15</td>
</tr>
<tr>
<td>Heart rate, BPM</td>
<td>72 ± 12</td>
<td>73 ± 12</td>
</tr>
<tr>
<td>NT-proBNP, median, pg/mL (IQR)</td>
<td>1631 (885–3154)</td>
<td>1594 (886–3305)</td>
</tr>
<tr>
<td>BNP, median, pg/mL (IQR)</td>
<td>255 (155–474)</td>
<td>251 (153–465)</td>
</tr>
<tr>
<td>History of DM, n (%)</td>
<td>1451 (34.7)</td>
<td>1456 (34.6)</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>Beta-blockers</td>
<td>3899 (93.1)</td>
<td>3912 (92.9)</td>
</tr>
<tr>
<td>MRAs</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>

BPM, beats per minute; CRT, cardiac resynchronization therapy; ICD, implantable cardioverter-defibrillator; IQR, interquartile range; SBP, systolic blood pressure.

*Mean ± standard deviation, unless stated.

PARADIGM-HF

Primary Endpoint: Time to First Occurrence of CV Death or HF Hospitalization

The difference in favor of sacubitril/valsartan was seen early in the trial and at each interim analysis.

HR: 0.80 (95% CI: 0.73–0.87)  
P<0.001  
20% Relative Risk Reduction

No. at risk

<table>
<thead>
<tr>
<th></th>
<th>Sac/val</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>

CI, confidence interval; HR, hazard ratio.
### PARADIGM-HF

**Summary of Key Findings**

<table>
<thead>
<tr>
<th>Endpoint</th>
<th>Sac/Val N=4187 n (%)</th>
<th>Enalapril N=4212 n (%)</th>
<th>HR (95% CI)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Primary composite endpoint of CV death or HF hospitalization</td>
<td></td>
<td></td>
<td>0.80 (0.73–0.87)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>CV death as first event</td>
<td>914 (21.8)</td>
<td>1117 (26.5)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>HF hospitalization as first event</td>
<td>377 (9.0)</td>
<td>459 (10.9)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>537 (12.8)</td>
<td>658 (15.6)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Number of patients with eventsa</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CV deathb</td>
<td>558 (13.3)</td>
<td>693 (16.5)</td>
<td>0.80 (0.71–0.89)</td>
<td></td>
</tr>
<tr>
<td>HF hospitalizations</td>
<td>537 (12.8)</td>
<td>658 (15.6)</td>
<td>0.79 (0.71–0.89)</td>
<td></td>
</tr>
<tr>
<td>All-cause mortality</td>
<td>711 (17.0)</td>
<td>835 (19.8)</td>
<td>0.84 (0.76–0.93)</td>
<td>0.0009</td>
</tr>
</tbody>
</table>

*a Analyses of the components of the primary composite endpoint were not prospectively planned to be adjusted for multiplicity.

*b Includes subjects who had HF hospitalization prior to death.

Entresto (sacubitril/valsartan) [package insert]. East Hanover, NJ: Novartis Pharmaceuticals Corp; August 2015.
Pharmacological Treatment for Stage C HFrEF: Recommendations

Recommendations for Renin-Angiotensin System Inhibition With ACE Inhibitor or ARB or ARNI (cont’d)

<table>
<thead>
<tr>
<th>COR</th>
<th>LOE</th>
<th>Recommendations</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>ARNI: B-R</td>
<td>In patients with chronic symptomatic HFrEF NYHA class II or III who tolerate an ACE inhibitor or ARB, replacement by an ARNI is recommended to further reduce morbidity and mortality.</td>
</tr>
</tbody>
</table>

“In patients with mild-to-moderate HF (characterized by either [1] mildly elevated natriuretic peptide levels, BNP [B-type natriuretic peptide] >150 pg/mL or NT-proBNP [N-terminal pro-B-type natriuretic peptide] ≥600 pg/mL; or [2] BNP ≥100 pg/mL or NT-proBNP ≥400 pg/mL with a prior hospitalization in the preceding 12 months) who were able to tolerate both a target dose of enalapril (10 mg twice daily) and then subsequently an ARNI (valsartan/sacubitril, 200* mg twice daily, with the ARB component equivalent to valsartan 160 mg), hospitalizations and mortality were significantly decreased with the valsartan/sacubitril compound compared with enalapril.”

*Dosing in clinical trials was based on the total amount of both components of sacubitril/valsartan, i.e., 24/26 mg, 49/51 mg, and 97/103 mg were referred to as 50 mg, 100 mg, and 200 mg, respectively.
ARNI, angiotensin receptor-neprilysin inhibitor
Comprehensive Receptor Blockade

- Maximum dose (determined by BNP and/or guidelines) of
  - Sacubitril/valsartan
  - + Beta blocker (metoprolol succinate, carvedilol, bisoprolol)
  - + Mineralocorticoid antagonist (spironolactone)

- Optimal diuretic therapy
BNP in outpatient management

- Ouwerkerk, et al. *JACC* 2018; 71: 386-98, Jan 30, 2018
- 2,516 patients with worsening heart failure from the BIOSTAT-CHF study compared with 3 theoretical treatment scenarios
  - A. All patients up-titrated to >50% of recommended doses
  - B. Patients up-titrated according to biomarker selection model
  - C. No patient is up-titrated to >50% of recommended doses
- Outcome measures: death or heart failure hospitalization
- Assessment: 161 biomarkers
BNP in outpatient management

• Results

• Guideline-based up titration
  • ACEi/ARB
  • B Blocker
  • MRA

• Biomarker based up titration
  • ACEi/ARB
  • B Blocker
  • MRA
Guideline based targets (AHA, ESC)

- **ACEi**
  - Enalapril: 10-20 mg BID
  - Lisinopril: 20-40 mg daily (ESC 20-35)

- **ARB**
  - Losartan: 150 mg

- **Beta blocker**
  - Metoprolol succ.: 200 mg

- **MRA**
  - Spironolactone: 50 mg
• Results
  • A biomarker-based treatment up titration choice in patients with heart failure was favorable over up titration to >50% recommended ACEi/ARB and beta blocker and over ≥50% MRA
  • However, differences were small between the 2 up titration groups.

• RECOMMENDATION. Up titration should always be attempted in heart failure patients
Use of sacubitril/valsartan

• Sangaralingham LR, et al. Circ H Fail 2018;11: e004302

• ARNI was approved by the FDA July 2015
• Its adoption and prescription costs were assessed in the next 18 months
• Large US insurance database + Medicare Advantage
  • 2244 patients initiated ARNI (3%)
  • Cost
    Health plan   $328.37
    Out of pocket $71.10, median $40.27
  • Adherence at 180 days 59.1%
ARNI and SCD
ARNI and Sudden Cardiac Death


Prospectively included 120 patients with ICD and EF < 40%

For 9 months, 100% ACEi or ARB + Beta blockers + MRA

After 9 months, ACEi or ARB was changed to sac/valsartan, followed for 9 months.

Analysis:

Appropriate shocks, NS-VT. PVC burden, BiV pacing percentage.
ARNI and Sudden Cardiac Death

• Results
  • Age 69 ± 8 years
  • LV EF 30.4%, 82% ischemic
  • Use of B-blockers (98%), MRA (97%) and AAD similar before & after sacubitril/valsartan

• Outcomes
  • NS-VT 15 ± 1.7 5.4 ± 0.5
  • Appropriate ICD 6.7% 0.8%
  • PVCs per hour 78 ± 15% 33 ± 12
  • BiV pacing 95 ± 6% 98.8 ± 1.3%
ARNI and Sudden Cardiac Death

- Why would ARNI reduce ventricular arrhythmias?
  - ARNI suppresses cardiac fibrosis and remodeling compared to ACEi alone
  - Natriuretic peptide levels translate the degree of myocardial stress, are associated with changes in electrophysiologic properties
  - Natriuretic peptide decreases sympathetic tone
Stroke risk in patients with HFrEF

• Meta-analysis of 4 trials. 22,904 patients with myocardial infarction without A Fib
• Follow up of 1.9 years. 660 patients had a stroke. (2.9%)
• Final stroke risk model
  • Older age
  • Killip Class 3 or 4 MI
  • eGFR ≤ 45 ml/min/1.73 m²
  • Hypertension history
  • History of previous stroke
CENTRAL ILLUSTRATION: Stroke Risk Score for Patients With MI Complicated With Systolic Dysfunction and/or HF

Stroke Risk Score

- Age, years
  - 60-75 = 2
  - >75 = 3
- Killip class
  - 3 or 4 = 1
- MI with EF ≤35% without AF
- Previous stroke
  - Yes = 3
- Hypertension
  - Yes = 1
- eGFR, ml/min/
  - 1.73 m²
  - 30-45 = 1

Maximum score = 11 points

Patients with ≥3 points have similar risk as those with AF

Pulmonary vein isolation for HF + AF

• Atrial fibrillation and heart failure commonly occur together, with atrial fibrillation increasing the risk for stroke, hospitalization for heart failure and death.
Pulmonary vein isolation for HF + AF

• Atrial fibrillation and heart failure commonly occur together, with atrial fibrillation increasing the risk for stroke, hospitalization for heart failure and death.
• Rhythm control with antiarrhythmic drugs is not superior to rate control in patients with atrial fibrillation.
Pulmonary vein isolation for HF + AF

- Atrial fibrillation and heart failure commonly occur together, with atrial fibrillation increasing the risk for stroke, hospitalization for heart failure and death.
- Rhythm control with antiarrhythmic drugs is not superior to rate control in patients with atrial fibrillation.
- Catheter ablation is well-established as a treatment for atrial fibrillation in patients with normal LV function, and there is some evidence of benefit in patients with heart failure.
CASTLE-AF. Catheter ablation vs standard conventional therapy in patients with LV dysfunction and atrial fibrillation.

- Patients with paroxysmal or chronic atrial fibrillation and
  - LV EF < 35%
  - AICD
  - Standard therapy for HF

Randomized to:
- Pulmonary vein isolation - 179 patients
- Medical therapy (rate/rhythm control) - 184 patients
Outcomes of CASTLE-AF. NEJM Feb 1, 2018
Table 2. Primary and Secondary Clinical End Points.*

<table>
<thead>
<tr>
<th>End Point</th>
<th>Ablation (N=179)</th>
<th>Medical Therapy (N=184)</th>
<th>Hazard Ratio (95% CI)</th>
<th>P Value Cox Regression</th>
<th>P Value Log-Rank Test</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>number (percent)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Primary†</td>
<td>51 (28.5)</td>
<td>82 (44.6)</td>
<td>0.62 (0.43–0.87)</td>
<td>0.007</td>
<td>0.006</td>
</tr>
<tr>
<td>Secondary</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Death from any cause</td>
<td>24 (13.4)</td>
<td>46 (25.0)</td>
<td>0.53 (0.32–0.86)</td>
<td>0.01</td>
<td>0.009</td>
</tr>
<tr>
<td>Heart-failure hospitalization</td>
<td>37 (20.7)</td>
<td>66 (35.9)</td>
<td>0.56 (0.37–0.83)</td>
<td>0.004</td>
<td>0.004</td>
</tr>
<tr>
<td>Cardiovascular death</td>
<td>20 (11.2)</td>
<td>41 (22.3)</td>
<td>0.49 (0.29–0.84)</td>
<td>0.009</td>
<td>0.008</td>
</tr>
<tr>
<td>Cardiovascular hospitalization</td>
<td>64 (35.8)</td>
<td>89 (48.4)</td>
<td>0.72 (0.52–0.99)</td>
<td>0.04</td>
<td>0.04</td>
</tr>
<tr>
<td>Hospitalization for any cause</td>
<td>114 (63.7)</td>
<td>122 (66.3)</td>
<td>0.99 (0.77–1.28)</td>
<td>0.96</td>
<td>0.96</td>
</tr>
<tr>
<td>Cerebrovascular accident</td>
<td>5 (2.8)</td>
<td>11 (6.0)</td>
<td>0.46 (0.16–1.33)</td>
<td>0.15</td>
<td>0.14</td>
</tr>
</tbody>
</table>

* All numbers and percentages represent the total numbers of events and raw event rates after a median follow-up of 37.8 months. Deaths and cerebrovascular accidents were evaluated at baseline and 12 weeks after baseline for hospitalizations in the two groups (the “blanking period”). For Kaplan–Meier estimates at 12, 36, and 60 months, see Table S6 in the Supplementary Appendix.
† The primary end point is a composite of death from any cause or hospitalization for worsening heart failure.
Underutilization of CAD Testing among patients hospitalized with new onset HF

- Retrospective cohort study of 67,161 patients with new onset HF

  - Only 17.5% had testing for ischemic CAD during index hospitalization, increasing to 27.4% at 90 days
  - Only 2.1% underwent revascularization during index hospitalization, increasing to 4.3% at 90 days

- ACC/AHA 2013 guidelines designate Class IIa indication to noninvasive and invasive assessment of ischemic CAD in HF patients.
CENTRAL ILLUSTRATION: Ischemic Work-Up in HF

A. Use of Noninvasive Imaging Among Patients Hospitalized for New-onset Heart Failure

B. Use of Invasive Testing Among Patients Hospitalized for New-onset Heart Failure

My epiphany about management of HFrEF

• We already have multiple effective treatments for heart failure with reduced EF.

• Before we clamor for new treatment modalities, we should optimize the therapies we now have available
Take home points

• Entresto (sacubitril/valsartan)
  • Comprehensive receptor blockade
  • Achieve goal-directed treatment for all patients
    • Sacubitril/valsartan (or ACE-i/ARB)
    • Beta-blocker
    • Spironolactone

• Consider stroke risk for patient in NSR post-MI with LV EF < 35%
• Catheter ablation for atrial fibrillation and LVEF < 35%
• Test for coronary artery disease in new onset heart failure