PIioneer-HF TRIal
FINDINGS AND SIGNIFICANCE
FEBRUARY 26, 2019

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Disclosures: Dr. Fonarow has consulted for Abbott, Amgen, Janssen, Medtronic, and Novartis, and has received research grants from the National Institutes of Health (NIH).
Heart failure (HF) is a major public health problem resulting in substantial morbidity, mortality, and healthcare expenditures. Despite available effective treatments, a large number of eligible patients are not receiving optimal care. Even with conventional therapy patients remain at risk for disease progression and adverse outcomes.

### Scope of Heart Failure

<table>
<thead>
<tr>
<th>Prevalence</th>
<th>Incidence</th>
<th>Mortality</th>
<th>Hospital Discharges</th>
<th>Cost</th>
</tr>
</thead>
<tbody>
<tr>
<td>6,500,000</td>
<td>1,000,000</td>
<td>308,976 (50% at 5 years)</td>
<td>900,000</td>
<td>$30.7 billion</td>
</tr>
</tbody>
</table>

American Heart Association. 2018 Heart and Stroke Statistical Update. Dallas, Tex: American Heart Association; 2018
Neurohormonal Activation in Heart Failure

Myocardial injury to the heart (CAD, HTN, CMP, valvular disease)
Initial fall in LV performance, ↑ wall stress

Activation of RAAS and SNS

- Remodeling and progressive worsening of LV function
- Fibrosis, apoptosis, hypertrophy, cellular/molecular alterations, myotoxicity
- Peripheral vasoconstriction, Hemodynamic alterations
- Heart failure symptoms: Fatigue, Activity altered, Chest congestion, Edema, Shortness of breath
- Morbidity and mortality, Arrhythmias, Pump failure

RAAS = renin-angiotensin-aldosterone system; SNS = sympathetic nervous system;
CMP = cardiomyopathy.
Life-Prolonging Medical Therapy

- ACE inhibitors or ARB (Class I, evidence A) in all patients without contraindications or intolerance.

- Evidence-based beta-blockers (Class I, evidence A) in all patients without contraindications or intolerance. This would include carvedilol (immediate or extended release), metoprolol succinate, or bisoprolol.

- Aldosterone antagonists (Class I, evidence A) in all patients with Class II–IV HF without contraindications or intolerance when close monitoring can be ensured.

Pharmacologic Treatment for Stage C HFrEF

HFrEF Stage C
NYHA Class I–IV

Treatment:

- Class I, LOE A
  - ACEI or ARB AND Beta-blocker

For persistently symptomatic African Americans, NYHA Class III–IV

- Class I, LOE A
  - Hydral-Nitrates

For all volume overload, NYHA Class II–IV patients

- Class I, LOE C
  - Loop Diuretics

For NYHA Class II–IV patients. Provided estimated creatinine >30 mL/min and K+ <5.0 mEq/dL

- Class I, LOE A
  - Aldosterone Antagonist

Residual Risk for HFrEF Despite Conventional GDMT

In PARADIGM-HF, study patients were followed over a median of 27 months.²,*

Of all patients randomized to enalapril, the absolute risk of CV death as a first event was 10.9% (n=459/4212)¹

*Adult patients with NYHA class II–IV symptoms and an ejection fraction of 40% or less were required to take a stable dose of a beta blocker and an ACE inhibitor (or ARB) equivalent to at least 10 mg of enalapril daily, with most also receiving MRA.

Long-term prognosis with hospitalization with HF is poor, irrespective of EF
When medications were prescribed, few patients were receiving target doses of ACEI/ARB (17%), ARNI (14%), and beta-blocker (28%), whereas most patients were receiving target doses of MRA therapy (77%).

Among patients eligible for all classes of medication, 1% were simultaneously receiving target doses of ACE/ARB/ARNI, beta-blocker, and MRA.
Patients Leaving the Hospital on GDMT Have Improved Treatment Adherence and Outcomes

*Initiation of a beta-blocker did not affect length of stay (LoS).¹

ACE, angiotensin-converting enzyme; ARB, angiotensin receptor blocker; GDMT, guideline-directed medical therapy; GWTG-HF, Get With The Guidelines®-Heart Failure; OPTIMIZE-HF, Organized Program to Initiate Lifesaving Treatment in Hospitalized Patients with Heart Failure.

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

Neprilysin inhibition

Neurohormonal activation
Vascular tone
Cardiac fibrosis, hypertrophy
Sodium retention

Sacubitril/Valsartan (LCZ696)

Mechanism of Action

Heart Failure

Angiotensinogen

Renin

Ang I

ACE

Ang II

AT1R

Natriuretic Peptides

Bradykinin

Substance P

Ang I-II

Vasodilation

Nephrilysin

LCZ696

Angiotensinogen

SODIUM RETENTION
VOLUME EXPANSION
VSMC GROWTH
VASOCONSTRICION
LV DYSFUNCTION
MYOCARDIAL FIBROSIS
MYOCARDIAL HYPERTROPHY

Inactive Metabolites

Aldosterone

Diuresis
Natriuresis
Vasodilation
Decreased myocardial remodeling
Aim of the PARADIGM-HF Trial

**Prospective comparison of ARNI with ACEI to Determine Impact on Global Mortality and morbidity in Heart Failure trial (PARADIGM-HF)**

Sacubitril/Valsartan 97/103 mg twice daily  
Enalapril 10 mg twice daily

SPECIFICALLY DESIGNED TO REPLACE CURRENT USE OF ACE INHIBITORS AND ANGIOTENSIN RECEPTOR BLOCKERS AS THE CORNERSTONE OF THE TREATMENT OF HEART FAILURE
PARADIGM-HF Trial: Design

Entry Criteria:

- NYHA Class II-IV HF, LVEF $\leq 40\%$ → amended to $\leq 35\%$
- BNP $\geq 150 \text{ pg/mL}$ (or NT-proBNP $\geq 600 \text{ pg/mL}$) or $1/3$ lower if hospitalized for HF within 12 mos
- On a stable dose of ACEI or ARB equivalent to $\geq 10 \text{ mg}$ of enalapril daily for $\geq 4$ weeks
- Unless contraindicated, on stable dose of beta-blocker for $\geq 4$ weeks
- SBP $\geq 95 \text{ mm Hg}$, eGFR $\geq 30 \text{ mL/min/1.73 m}^2$ and serum K $\leq 5.4 \text{ mmol/L}$ at randomization

Sac/Val = Sacubitril/Valsartan.


Primary endpoint: Death from CV causes or hospitalization for HF
PARADIGM-HF: Primary Endpoint of CV Death or Heart Failure Hospitalization

Number needed to treat = 21

HR 0.80 (95% CI, 0.73–0.87), p<0.001

Sac/Val = Sacubitril/Valsartan.

### PARADIGM-HF: Effect of Sac/Val vs. Enalapril on the Primary Endpoint and Its Components

<table>
<thead>
<tr>
<th></th>
<th>Sac/Val (n=4187)</th>
<th>Enalapril (n=4212)</th>
<th>Hazard Ratio (95% CI)</th>
<th>( p )-Value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Primary endpoint</strong></td>
<td>914 (21.8%)</td>
<td>1117 (26.5%)</td>
<td>0.80 (0.73–0.87)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td><strong>Cardiovascular death</strong></td>
<td>558 (13.3%)</td>
<td>693 (16.5%)</td>
<td>0.80 (0.71–0.89)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td><strong>Hospitalization for heart failure</strong></td>
<td>537 (12.8%)</td>
<td>658 (15.6%)</td>
<td>0.79 (0.71–0.89)</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

Sac/Val = Sacubitril/Valsartan.

PARADIGM-HF: All-Cause Mortality

HR 0.84 (95% CI, 0.76–0.93), p<0.001

Number needed to treat = 36

PCRADIGM-HF: All-Cause Mortality

HR 0.84 (95% CI, 0.76–0.93), p<0.001

Number needed to treat = 36

Sac/Val = Sacubitril/Valsartan.

Sac/Val vs. Enalapril on Primary Endpoint and on CV Death by Subgroups

<table>
<thead>
<tr>
<th>Subgroup</th>
<th>Sac/Val No.</th>
<th>Enalapril No.</th>
<th>Primary Endpoint Hazard Ratio (95% CI)</th>
<th>p-Value for Interaction</th>
<th>Death from Cardiovascular Causes Hazard Ratio (95% CI)</th>
<th>p-Value for Interaction</th>
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</thead>
<tbody>
<tr>
<td>All Patients</td>
<td>4187</td>
<td>4212</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;65 years</td>
<td>2111</td>
<td>2168</td>
<td></td>
<td>0.47</td>
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<td>0.70</td>
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<tr>
<td>≥65 years</td>
<td>2076</td>
<td>2044</td>
<td></td>
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<tr>
<td>Sex</td>
<td></td>
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<td></td>
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<tr>
<td>Male</td>
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<td>3259</td>
<td></td>
<td>0.63</td>
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<td>879</td>
<td>953</td>
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<td>I or II</td>
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<td>0.03</td>
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<td>III or IV</td>
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<td>1076</td>
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<tr>
<td>Estimated GFR</td>
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<tr>
<td>&lt;60 mL/min/1.73 m²</td>
<td>1541</td>
<td>1520</td>
<td></td>
<td>0.91</td>
<td></td>
<td>0.73</td>
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<tr>
<td>≥60 mL/min/1.73 m²</td>
<td>2646</td>
<td>2692</td>
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<tr>
<td>Ejection fraction</td>
<td></td>
<td></td>
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<tr>
<td>≤35%</td>
<td>3715</td>
<td>3722</td>
<td></td>
<td>0.36</td>
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<tr>
<td>&gt;35%</td>
<td>472</td>
<td>489</td>
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<td>NT-proBNP</td>
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<tr>
<td>≤Median</td>
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<td>0.16</td>
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<td>0.33</td>
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<tr>
<td>&gt;Median</td>
<td>2103</td>
<td>2087</td>
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<td>Hypertension</td>
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<td>2971</td>
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<td></td>
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<tr>
<td>Prior use of ACE inhibitor</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>No</td>
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<td>946</td>
<td></td>
<td>0.09</td>
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<td>0.06</td>
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<tr>
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<td>3266</td>
<td>3266</td>
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<tr>
<td>Prior use of aldosterone antagonist</td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>No</td>
<td>1916</td>
<td>1812</td>
<td></td>
<td>0.10</td>
<td></td>
<td>0.32</td>
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<td>Yes</td>
<td>2271</td>
<td>2400</td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Prior hospitalization for heart failure</td>
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<td></td>
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<tr>
<td>No</td>
<td>1580</td>
<td>1545</td>
<td></td>
<td>0.10</td>
<td></td>
<td>0.19</td>
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<tr>
<td>Yes</td>
<td>2607</td>
<td>2667</td>
<td></td>
<td></td>
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<td></td>
</tr>
</tbody>
</table>

Effect of Sacubitril/Valsartan on Early and Late Measures of HF Progression

### Hospitalization for HF in First 30 Days

<table>
<thead>
<tr>
<th>Patients at Risk</th>
<th>Days after Randomization</th>
<th>Patients at Risk</th>
<th>Days after Randomization</th>
</tr>
</thead>
<tbody>
<tr>
<td>LCZ696</td>
<td>4187</td>
<td>Enalapril</td>
<td>4212</td>
</tr>
<tr>
<td></td>
<td>4174</td>
<td></td>
<td>4192</td>
</tr>
<tr>
<td></td>
<td>4153</td>
<td></td>
<td>4166</td>
</tr>
<tr>
<td></td>
<td>4140</td>
<td></td>
<td>4143</td>
</tr>
</tbody>
</table>

Hazard ratio 0.60 (0.38-0.94)

P = 0.027

### Cumulative Hospitalizations

<table>
<thead>
<tr>
<th>Patients at Risk</th>
<th>Days after Randomization</th>
<th>Patients at Risk</th>
<th>Days after Randomization</th>
</tr>
</thead>
<tbody>
<tr>
<td>LCZ696</td>
<td>4187</td>
<td>Enalapril</td>
<td>4212</td>
</tr>
<tr>
<td></td>
<td>4054</td>
<td></td>
<td>4049</td>
</tr>
<tr>
<td></td>
<td>3885</td>
<td></td>
<td>3857</td>
</tr>
<tr>
<td></td>
<td>3276</td>
<td></td>
<td>3228</td>
</tr>
<tr>
<td></td>
<td>2472</td>
<td></td>
<td>2408</td>
</tr>
<tr>
<td></td>
<td>1710</td>
<td></td>
<td>1724</td>
</tr>
<tr>
<td></td>
<td>1001</td>
<td></td>
<td>993</td>
</tr>
<tr>
<td></td>
<td>279</td>
<td></td>
<td>278</td>
</tr>
<tr>
<td></td>
<td>12</td>
<td></td>
<td>17</td>
</tr>
</tbody>
</table>

Rate ratio 0.77 (0.67-0.88)

P < 0.001

Pharmacological Treatment for Stage C HFrEF

| Recommendations for Renin-Angiotensin System Inhibition With ACE Inhibitor or ARB or ARNI |
|-----------------|---------------------------------------------------------------------------------------------------------------------------------|
| COR | LOE | Recommendations                                                                                                                  |
| I   | ACE: A | 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. |
| I   | ARB: A |                                                                                                                                     |
| I   | ARNI: B-R |                                                                                                                                   |
| III: Harm | B-R | ARNI should not be administered concomitantly with ACE inhibitors or within 36 hours of the last dose of an ACE inhibitor (31, 32). |
| III: Harm | C-EO | ARNI should not be administered to patients with a history of angioedema.                                                          |

ARNI = angiotensin receptor blocker and nepri lysin inhibitor; COR = class of recommendation; LOE = level of evidence.

Influence of Sacubitril/Valsartan on Readmission Rates After HF Hospitalization: PARADIGM-HF

2,383 investigator-reported HF hospitalizations, of which 1,076 (45.2%) occurred in subjects assigned to sacubitril/valsartan and 1,307 (54.8%) occurred in subjects assigned to enalapril.

GWTG-HF Data on ACEI/ARB or ARNI at Discharge*

Percent of heart failure patients with left ventricular systolic dysfunction (LVSD) and without angiotensin converting enzyme inhibitor (ACEI) and angiotensin receptor blocker (ARB) or angiotensin-receptor/neprilysin inhibitor (ARNI) contraindications who are prescribed an ACEI, ARB, or ARNI at hospital discharge.

Time Period: 01/2010 - 01/2019

<table>
<thead>
<tr>
<th>Benchmark Group</th>
<th>Time Period</th>
<th>Numerator</th>
<th>Denominator</th>
<th>% of Patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>All Hospitals</td>
<td>2010</td>
<td>35947</td>
<td>37974</td>
<td>94.7%</td>
</tr>
<tr>
<td>All Hospitals</td>
<td>2011</td>
<td>36960</td>
<td>38791</td>
<td>95.3%</td>
</tr>
<tr>
<td>All Hospitals</td>
<td>2012</td>
<td>35702</td>
<td>37215</td>
<td>95.9%</td>
</tr>
<tr>
<td>All Hospitals</td>
<td>2013</td>
<td>35615</td>
<td>37036</td>
<td>96.2%</td>
</tr>
<tr>
<td>All Hospitals</td>
<td>2014</td>
<td>35677</td>
<td>37029</td>
<td>96.3%</td>
</tr>
<tr>
<td>All Hospitals</td>
<td>2015</td>
<td>36394</td>
<td>38728</td>
<td>94.0%</td>
</tr>
<tr>
<td>All Hospitals</td>
<td>2016</td>
<td>37913</td>
<td>40498</td>
<td>93.6%</td>
</tr>
<tr>
<td>All Hospitals</td>
<td>2017</td>
<td>38446</td>
<td>41558</td>
<td>92.5%</td>
</tr>
<tr>
<td>All Hospitals</td>
<td>2018</td>
<td>34270</td>
<td>37013</td>
<td>92.6%</td>
</tr>
<tr>
<td>All Hospitals</td>
<td>2019</td>
<td>481</td>
<td>509</td>
<td>94.5%</td>
</tr>
</tbody>
</table>
GWTG-HF Data Angiotensin Receptor-Neprilysin Inhibitor (ARNI) at Discharge

Percentage of eligible patients with heart failure who are prescribed an ARNI at hospital discharge.

Time Period: 01/2010 - 01/2019

<table>
<thead>
<tr>
<th>Benchmark Group</th>
<th>Time Period</th>
<th>Numerator</th>
<th>Denominator</th>
<th>% of Patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>All Hospitals</td>
<td>2010</td>
<td>0</td>
<td>35939</td>
<td>0.0%</td>
</tr>
<tr>
<td>All Hospitals</td>
<td>2011</td>
<td>0</td>
<td>37078</td>
<td>0.0%</td>
</tr>
<tr>
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<td>2012</td>
<td>0</td>
<td>35636</td>
<td>0.0%</td>
</tr>
<tr>
<td>All Hospitals</td>
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<td>0</td>
<td>35487</td>
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</tr>
<tr>
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<td>2014</td>
<td>1</td>
<td>35046</td>
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</tr>
<tr>
<td>All Hospitals</td>
<td>2015</td>
<td>83</td>
<td>34393</td>
<td>0.2%</td>
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<tr>
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<td>2016</td>
<td>1456</td>
<td>32811</td>
<td>4.4%</td>
</tr>
<tr>
<td>All Hospitals</td>
<td>2017</td>
<td>3502</td>
<td>36090</td>
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<tr>
<td>All Hospitals</td>
<td>2018</td>
<td>4402</td>
<td>26416</td>
<td>16.7%</td>
</tr>
<tr>
<td>All Hospitals</td>
<td>2019</td>
<td>82</td>
<td>373</td>
<td>22.0%</td>
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</tbody>
</table>
Angiotensin Receptor-Neprilysin Inhibition in Patients Hospitalized With Acute Decompensated Heart Failure

Eric J Velazquez,1 David A Morrow,2 Adam D DeVore,3 Carol I Duffy,4 Andrew P Ambrosy,3 Kevin McCague,4 Ricardo Rocha,4 Eugene Braunwald2

1Yale Univ Sch of Med, New Haven, CT; 2Harvard Univ/Brigham and Women's Hosp, Boston, MA; 3Duke Univ/Duke Clinical Res Inst, Durham, NC; 4Novartis Pharmaceuticals Corp, East Hanover, NJ; 5
Background

- Acute decompensated heart failure (ADHF) accounts for over 1M hospitalizations in the US annually
- Guideline-directed therapy for ADHF is limited
  - Decongestion with diuretics and hemodynamic support with vasodilators remain the standards of care
Rationale

- PARADIGM-HF trial in chronic HFrEF: sacubitril/valsartan → CV death or HF hospitalization compared to enalapril
  - Patients with ADHF requiring IV therapy were excluded
  - Stable HF therapy with adequate doses for >4 weeks
  - Required sequential run-in with high dose enalapril and sacubitril/valsartan before randomization

- It is unknown if in-hospital initiation of sacubitril/valsartan compared to enalapril is safe and effective in ADHF

McMurray JJ. NEJM. 2014;371:993-1004.
Study Design

Hospitalized with ADHF (HFrEF) → Stabilized

- Evaluate biomarker surrogates of efficacy
- Evaluate safety and tolerability
- Explore clinical outcomes

Titration algorithm over 8 weeks

sacubitril/valsartan vs enalapril
Key Entry Criteria

- Hospitalized for ADHF (signs and symptoms of fluid overload)
- LVEF ≤40% within the last 6 months
- NT-proBNP ≥1600 pg/mL or BNP ≥400 pg/mL (screening)
- Stabilized while still hospitalized
  - In the prior 6 hours:
    - SBP ≥100 mmHg, no symptomatic hypotension
    - No increase in IV diuretics
    - No IV vasodilators
  - In the prior 24 hours: no IV inotropes
Key Endpoints

- **Primary endpoint:** Proportional change in NT-proBNP from baseline to the mean of weeks 4 and 8

- **Safety**
  - Worsening renal function
  - Hyperkalemia
  - Symptomatic hypotension
  - Angioedema

- **Exploratory Clinical Outcomes**
  - Serious clinical composite: death, re-hospitalization for HF, LVAD, or listing for cardiac transplant
  - Expanded composite: Serious composite + addition of HF med, unplanned outpatient IV diuretics or >50% increase in dose
SBP Dose Titration Algorithm

- Starting dose level based on SBP
  - If 100 to <120 mm Hg, sacubitril/valsartan 24/26 mg or enalapril 2.5 mg twice daily
  - If ≥120 mm Hg, sacubitril/valsartan 49/51 mg or enalapril 5 mg twice daily
- Up-titration based on SBP (clinical judgement permitted)
- Target doses
  - sacubitril/valsartan 97/103 mg twice daily or enalapril 10 mg twice daily
## Baseline Characteristics

<table>
<thead>
<tr>
<th></th>
<th>sacubitril/valsartan (n=440)</th>
<th>enalapril (n=441)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age* (years)</td>
<td>61 (51, 71)</td>
<td>63 (54, 72)</td>
</tr>
<tr>
<td>Women (%)</td>
<td>25.7</td>
<td>30.2</td>
</tr>
<tr>
<td>Black (%)</td>
<td>35.9</td>
<td>35.8</td>
</tr>
<tr>
<td>No prior HF diagnosis (%)</td>
<td>32.3</td>
<td>37.0</td>
</tr>
<tr>
<td>No ACEi/ARB therapy (%)</td>
<td>52.7</td>
<td>51.5</td>
</tr>
<tr>
<td>LVEF*</td>
<td>0.24 (0.18, 0.30)</td>
<td>0.25 (0.20, 0.30)</td>
</tr>
<tr>
<td>SBP (mm Hg)*</td>
<td>118 (110, 133)</td>
<td>118 (109, 132)</td>
</tr>
<tr>
<td>NT-proBNP (pg/mL)*</td>
<td>2883 (1610, 5403)</td>
<td>2536 (1363, 4917)</td>
</tr>
</tbody>
</table>

*Median (interquartile range).*
Primary Endpoint: % Change in NT-proBNP

29% greater reduction with sacubitril/valsartan
CI 19%, 37%; P < 0.0001
## Safety

<table>
<thead>
<tr>
<th>Safety Events (%)</th>
<th>sacubitril/valsartan (n=440)</th>
<th>enalapril (n=441)</th>
<th>RR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Worsening renal function*</td>
<td>13.6</td>
<td>14.7</td>
<td>0.93 (0.67-1.28)</td>
</tr>
<tr>
<td>Hyperkalemia†</td>
<td>11.6</td>
<td>9.3</td>
<td>1.25 (0.84-1.84)</td>
</tr>
<tr>
<td>Symptomatic hypotension</td>
<td>15.0</td>
<td>12.7</td>
<td>1.18 (0.85-1.64)</td>
</tr>
<tr>
<td>Angioedema event</td>
<td>1 (0.2%)</td>
<td>6 (1.4%)</td>
<td>0.17 (0.02-1.38)</td>
</tr>
</tbody>
</table>

P = NS for all safety events

*Cr ≥0.5 with simultaneous reduction in eGFR of ≥25%

†K+ >5.5 mg/dl
Serious Composite Clinical Endpoint

Death, HF re-hosp, LVAD, Transplant listing

HR = 0.54; 95% CI 0.37, 0.79
P = 0.001
NNT = 13

enalapril
N = 441
16.8%
sacubitril/valsartan
N = 440
9.3%
# Exploratory Clinical Endpoints

<table>
<thead>
<tr>
<th></th>
<th>sacubitril/ valsartan (n=440)</th>
<th>enalapril (n=441)</th>
<th>HR</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Serious Composite, %</strong></td>
<td>9.3</td>
<td>16.8</td>
<td>0.54</td>
<td>0.001</td>
</tr>
<tr>
<td><strong>Death, %</strong></td>
<td>2.3</td>
<td>3.4</td>
<td>0.66</td>
<td>0.311</td>
</tr>
<tr>
<td><strong>Re-hosp for HF, %</strong></td>
<td>8.0</td>
<td>13.8</td>
<td>0.56</td>
<td>0.005</td>
</tr>
<tr>
<td><strong>LVAD, %</strong></td>
<td>0.2</td>
<td>0.2</td>
<td>0.99</td>
<td>0.999</td>
</tr>
<tr>
<td><strong>Cardiac Transplant, %</strong></td>
<td>0</td>
<td>0</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td><em><em>Expanded Composite</em>, %</em>*</td>
<td>56.6</td>
<td>59.9</td>
<td>0.93</td>
<td>0.369</td>
</tr>
<tr>
<td><strong>Unplanned IV diuretics, %</strong></td>
<td>0.5</td>
<td>0.5</td>
<td>0.99</td>
<td>0.997</td>
</tr>
<tr>
<td><strong>Addition of HF med, %</strong></td>
<td>17.7</td>
<td>19.1</td>
<td>0.92</td>
<td>0.58</td>
</tr>
<tr>
<td><strong>&gt;50% diuretic increase, %</strong></td>
<td>49.6</td>
<td>50.3</td>
<td>0.98</td>
<td>0.812</td>
</tr>
</tbody>
</table>

*Serious composite + addition of HF med, no unplanned outpatient IV diuretics or >50% increase in dose
PIONEER-HF: Exploratory Clinical Outcomes
30-Day HF Readmission

HF Readmission Rate Through Day 30 (%)

- Sacubitril/Valsartan: 8.0% (n=440)
- Enalapril: 13.8% (n=441)

Relative Risk Reduction: 5.8%

HR: 0.56 (95% CI 0.37-0.84)  
P=0.005

*44% Absolute Risk Reduction
### Change in NT-proBNP

<table>
<thead>
<tr>
<th>Subgroup</th>
<th>sacubitril/valsartan vs. enalapril mean [95% CI]</th>
<th>Subgroup</th>
<th>Hazard Ratio [95% CI]</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>All Patients</strong></td>
<td>0.71 [0.63, 0.81]</td>
<td><strong>All Patients</strong></td>
<td>0.54 [0.37, 0.79]</td>
</tr>
<tr>
<td>Prior HF</td>
<td></td>
<td>Prior HF</td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>0.65 [0.53, 0.81]</td>
<td>No</td>
<td>0.37 [0.12, 1.15]</td>
</tr>
<tr>
<td>Yes</td>
<td>0.72 [0.63, 0.83]</td>
<td>Yes</td>
<td>0.53 [0.35, 0.80]</td>
</tr>
<tr>
<td>Prior ACEi/ARB</td>
<td></td>
<td>Prior ACEi/ARB</td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>0.72 [0.60, 0.86]</td>
<td>No</td>
<td>0.52 [0.29, 0.95]</td>
</tr>
<tr>
<td>Yes</td>
<td>0.72 [0.61, 0.85]</td>
<td>Yes</td>
<td>0.56 [0.34, 0.92]</td>
</tr>
</tbody>
</table>

### Serious Composite Endpoint

**Favors sacubitril / valsartan**

**Favors enalapril**

**P value (interaction) = NS**

**Note:**
- The hazard ratio for the serious composite endpoint is given for each subgroup.
- The interaction p-value for the change in NT-proBNP is non-significant (NS).
- The comparison between sacubitril/valsartan and enalapril is indicated by the hazard ratios and their confidence intervals.
Conclusions

Among hemodynamically stabilized acute heart failure patients with reduced EF, compared with enalapril, sacubitril/valsartan administered over 8 weeks …

- Led to greater reduction in NT-proBNP
- Reduced re-hospitalization for heart failure
- Was well tolerated with comparable rates of worsening renal function, hyperkalemia, symptomatic hypotension, and angioedema
Clinical Implications

These results support the in-hospital initiation of sacubitril/valsartan in stabilized patients with acute decompensated heart failure and reduced EF, irrespective of prior ACEi/ARB use, or prior HF diagnosis.
Angiotensin–Neprilysin Inhibition in Acute Decompensated Heart Failure

Eric J. Velazquez, M.D., David A. Morrow, M.D., M.P.H.,
Adam D. DeVore, M.D., M.H.S., Carol I. Duffy, D.O., Andrew P. Ambrosy, M.D.,
Kevin McCague, M.A., Ricardo Rocha, M.D., and Eugene Braunwald, M.D., for
the PIONEER-HF Investigators*
Practical Points on Use of Sacubitril/Valsartan

- Starting dose is 24/26 mg twice daily, unless patient is tolerating full dose ACEI or ARB in which case start 49/51 mg twice daily
- Target dose is 97/103 mg twice daily
- After 2-4 weeks uptitrate to next dose, aim for target dose
- In-hospital initiation is safe, well tolerated, and improves early outcomes
- Monitor SBP, renal function and K as you would with ACEI or ARB use
- Space out dosing from other vasoactive medications if needed
- Adjust diuretics doses based on volume status
2017 ACC Expert Consensus Decision Pathway for Optimization of Heart Failure Treatment

10 Principles for Successful Treatment of Heart Failure

How to implement GDMT...
I. Initiate & Switch
   Treatment algorithm for guideline-directed medical therapy including novel therapies (Figure 2 and 3)

II. Titration
   Target doses of select guideline-directed heart failure therapy (Tables 1, 2, 3, 4, 5)
   Considerations for monitoring

How to address challenges with...
III. Referral
   Triggers for referral to HF specialist (Table 6)

IV. Care Coordination
   Essential skills for a HF team (Table 7)
   Infrastructure for team-based HF care (Table 8)

V. Adherence
   Causes of non-adherence (Table 9)
   Interventions for adherence (Table 10, 11)

VI. Specific Patient Cohorts
   Evidence based recommendations and assessment of risk for special cohorts:
   African Americans; older adults; frail (Table 12)

VII. Cost of Care
   Strategies to reduce cost (Table 13)
   Helpful information for completion of prior authorization forms (Table 14)

How to manage...
VIII. Increasing Complexity
   Ten pathophysilogic targets in HFpEF and treatments (Table 15)
   Ten principles and actions to guide optimal therapy

IX. Comorbidities
   Common cardiac and non-cardiac comorbidities with suggested actions (Table 16)

X. Palliative/Hospice Care
   Seven principles and actions to consider regarding palliative care

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Treatment Algorithm for Guideline-Directed Medical Therapy Including Novel Therapies

Excerpted from:

Optimization of Heart Failure Treatment: Answers to 10 Pivotal Issues About Heart Failure with Reduced Ejection Fraction

December 2017
DOI: 10.1016/j.jacc.2017.11.025
## EVIDENCE-BASED HFREF THERAPIES

<table>
<thead>
<tr>
<th>Guideline Recommended Therapy</th>
<th>Relative Risk Reduction in Mortality</th>
<th>Number Needed to Treat for Mortality</th>
<th>NNT for Mortality (standardized to 36 months)</th>
<th>Relative Risk Reduction in HF Hospitalizations</th>
</tr>
</thead>
<tbody>
<tr>
<td>ACEI/ARB</td>
<td>17%</td>
<td>22 over 42 months</td>
<td>26</td>
<td>31%</td>
</tr>
<tr>
<td>ARNI</td>
<td>16%</td>
<td>36 over 27 months</td>
<td>27</td>
<td>21%</td>
</tr>
<tr>
<td>Beta-blocker</td>
<td>34%</td>
<td>28 over 12 months</td>
<td>9</td>
<td>41%</td>
</tr>
<tr>
<td>Aldosterone Antagonist</td>
<td>30%</td>
<td>9 over 24 months</td>
<td>6</td>
<td>35%</td>
</tr>
<tr>
<td>Hydralazine/Nitrate</td>
<td>43%</td>
<td>25 over 10 months</td>
<td>7</td>
<td>33%</td>
</tr>
<tr>
<td>CRT</td>
<td>36%</td>
<td>12 over 24 months</td>
<td>8</td>
<td>52%</td>
</tr>
<tr>
<td>ICD</td>
<td>23%</td>
<td>14 over 60 months</td>
<td>23</td>
<td>NA</td>
</tr>
<tr>
<td>Ivabradine</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>26%</td>
</tr>
</tbody>
</table>

Cost-Effectiveness and Value of Sacubitril/Valsartan Replacing Enalapril in HFrEF

- For every 100,000 people receiving sacubitril/valsartan, this strategy could potentially reduce hospitalizations by 3000 and reduce deaths by nearly the same number over a 2-year period. Medical savings from reduced HF admissions would be more than $27 million.

What Value Do You and Your Patients Place on Being Able to Live 1-2 Years on Average Longer?


Potential Mortality Reduction With Implementation of Sacubitril/Valsartan Therapy

**Potential Benefit**

- 5,700,000 patients with HF in the United States
  - 2,964,000 excluded with HFpEF

2,736,000 HFrEF

- 136,800 excluded
  - 109,440 in hospice or comfort care only
  - 27,360 receiving advanced therapies

2,599,200 HFrEF

- 311,904 excluded
  - 181,944 with contraindication for or intolerance to ACE inhibitor/ARB/ARNI
  - 129,960 with SBP <95 mm Hg

2,287,296 HFrEF eligible for ARNI

Optimal implementation of ARNI therapy was empirically estimated to prevent 28,484 (range, 18,230-41,017) deaths per year

**Actual Practice**

**ARNI Use in Eligible HFrEF Patients**

Relationship Between Hospital Characteristics and Early Adoption of Angiotensin-Receptor/Nephrilysin Inhibitor Among Eligible Patients Hospitalized for Heart Failure

Nancy Luo, MD; Steven J. Lippmann, PhD; Robert J. Mentz, MD; Melissa A. Greiner, MS; Bradley G. Hammill, DrPH; N. Chantelle Hardy, MPH; Warren K. Laskey, MD, MPH; Paul A. Heidenreich, MD, MS; Chun-Lin Chang, PhD; Adrian F. Hernandez, MD, MHS; Lesley H. Curtis, PhD; Pamela N. Peterson, MD, MSPH; Gregg C. Fonarow, MD; Emily C. O’Brien, PhD

Background—The angiotensin-receptor/nephrilysin inhibitor (ARNI) sacubitril/valsartan reduces hospitalization and mortality for patients with heart failure with reduced ejection fraction. However, adoption of ARNI into clinical practice has been slow. Factors influencing use of ARNI have not been fully elucidated. Using data from the Get With The Guidelines-Heart Failure registry, Hospital Compare, Dartmouth Atlas, and the American Hospital Association Survey, we sought to identify hospital characteristics associated with patient-level receipt of an ARNI prescription.

Methods and Results—We analyzed patients with heart failure with reduced ejection fraction who were eligible for ARNI prescription (ejection fraction ≤ 40%, no contraindications) and hospitalized from October 1, 2015 through December 31, 2016. We used logistic regression to estimate the associations between hospital characteristics and patient ARNI prescription at hospital discharge, accounting for clustering of patients within hospitals using generalized estimating equation methods and adjusting for patient-level covariates. Of 16,674 eligible hospitalizations from 210 hospitals, 1,020 patients (6.1%) were prescribed ARNI at discharge. The median hospital-level proportion of patients prescribed ARNI was 3.3% (IQR: 0.03%, 12.6%). After adjustment for patient-level covariates, for-profit hospitals had significantly higher odds of ARNI prescription compared with not-for-profit hospitals (odds ratio, 2.53; 95% CI, 1.05–6.10; P = 0.04), and hospitals located in the Western United States had lower odds of ARNI prescription compared with those in the Northeast (odds ratio, 0.33; 95% CI, 0.13–0.84; P = 0.02).

Conclusions—Relatively few hospital characteristics were associated with ARNI prescription at hospital discharge, in contrast to what has been observed in early adoption in other disease areas. Additional evaluation of barriers to implementing new evidence into heart failure practice is needed. (J Am Heart Assoc. 2019;8:e010484. DOI: 10.1161/JAHA.118.010484.)
HF Management Is Multidimensional

- **Lifestyle Changes/ Patient Education**
  - Weight loss
  - Smoking cessation
  - Low-sodium diet
  - Exercise training
  - Cardiac rehabilitation
  - Medication adherence
  - Symptom monitoring
  - Self-care

- **Guideline-Directed HF Therapies**
  - ACEIs/ARBs
  - β-Blockers
  - Aldosterone antagonists
  - ARNI
  - Funny channel inhibition
  - HYD/ISDN
  - Diuretics
  - Digoxin

- **Devices**
  - CRT
  - ICD
  - Ventricular assist devices

- **Transplantation in Advanced HF**
  - Gold standard for the treatment of refractory end-stage HF
  - 1-year posttransplant survival rate of 88%

- **Palliative Care**
  - Access to treatment and end-of-life care
  - Control of symptoms, psychological distress, and HRQOL
  - Advance directives
  - Caregiver support
  - Frailty/dementia assessments

## Potential Impact of Optimal Implementation of Evidence-Based HFrEF Therapies on Mortality in the US

<table>
<thead>
<tr>
<th>Guideline Recommended Therapy</th>
<th>HF Patient Population Eligible for Treatment, n*</th>
<th>Current HF Population Eligible and Untreated, n (%)</th>
<th>Potential Lives Saved per Year</th>
<th>Potential Lives Saved per Year (Sensitivity Range*)</th>
</tr>
</thead>
<tbody>
<tr>
<td>ACEI/ARB</td>
<td>2,459,644</td>
<td>501,767 (20.4)</td>
<td>6516</td>
<td>(3336-11,260)</td>
</tr>
<tr>
<td>ARNI (replacing ACEI/ARB)</td>
<td>2,287,296</td>
<td>2,287,296 (100)</td>
<td>28,484</td>
<td>(18,230-41,017)</td>
</tr>
<tr>
<td>Beta-blocker</td>
<td>2,512,560</td>
<td>361,809 (14.4)</td>
<td>12,922</td>
<td>(6616-22,329)</td>
</tr>
<tr>
<td>Aldosterone Antagonist</td>
<td>603,014</td>
<td>385,326 (63.9)</td>
<td>21,407</td>
<td>(10,960-36,991)</td>
</tr>
<tr>
<td>Hydralazine/Nitrate</td>
<td>150,754</td>
<td>139,749 (92.7)</td>
<td>6655</td>
<td>(3407-11,500)</td>
</tr>
<tr>
<td>CRT</td>
<td>326,151</td>
<td>199,604 (61.2)</td>
<td>8317</td>
<td>(4258-14,372)</td>
</tr>
<tr>
<td>ICD</td>
<td>1,725,732</td>
<td>852,512 (49.4)</td>
<td>12,179</td>
<td>(6236-21,045)</td>
</tr>
<tr>
<td>Total</td>
<td>-</td>
<td>-</td>
<td>96,480</td>
<td>(53,013-158,514)</td>
</tr>
</tbody>
</table>

CONCLUSIONS

• GWTG-HF is focused on improving on meaningful processes of care and patient-centered outcomes
• ACEI/Beta Blocker/MRA previously established as cornerstone of therapy in HFrEF
• ARNI further reduces morbidity and mortality
• PIONNER-HF provides important need insights into the safety and effectiveness of in-hospital initiation of ARNI in eligible patients
• In-hospital initiation of ARNI and other GDMT improves outcomes
• Every effort should be made to optimize use and dosing of GDMT in all settings in which these patients are cared for
CONTACT US TO LEARN MORE

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Thank You For Your Active Participation And Contributions To GWTG-Heart Failure!