Advances in the Management of Heart Failure

SPEAKER
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Heart Failure Background

- Heart failure (HF) is a major public health problem resulting in substantial morbidity, mortality, and healthcare expenditures
- Major cost-driver of HF is high incidence of hospitalizations
- Despite treatment advances large number of eligible patients are not receiving one or more evidence-based HF therapies

<table>
<thead>
<tr>
<th>Population Group</th>
<th>Prevalence</th>
<th>Incidence</th>
<th>Mortality</th>
<th>Hospital Discharges</th>
<th>Cost</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total population</td>
<td>6,500,000</td>
<td>1,000,000</td>
<td>368,976</td>
<td>900,000</td>
<td>$30.7 billion</td>
</tr>
</tbody>
</table>

Survival after the onset of heart failure in Framingham Heart Study subjects

- Women: 5-year mortality 50%
- Men: 5-year mortality 30%

Outcomes During and After HF Hospitalization

- In-hospital
  - Length of stay (mean) 6.2 days
  - Mortality rate 4.1%
- Hospital readmissions
  - 20% at 30 days
  - 50% at 6 months
- Longer-term mortality
  - 11.6% at 30 days
  - 33.1% at 12 months

**Approach to the Classification of Heart Failure**

<table>
<thead>
<tr>
<th>Stage</th>
<th>Patient Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>High risk for developing heart failure (HF) - Hypertension - CAD - Diabetes mellitus - Family history of cardiomyopathy</td>
</tr>
<tr>
<td>B</td>
<td>Asymptomatic HF - Previous MI - LV systolic dysfunction - Asymptomatic valvular disease</td>
</tr>
<tr>
<td>C</td>
<td>Symptomatic HF - Known structural heart disease - Shortness of breath and fatigue - Reduced exercise tolerance</td>
</tr>
<tr>
<td>D</td>
<td>Refractory end-stage HF - Marked symptoms at rest despite maximal medical therapy (e.g., those who are recurrently hospitalized or cannot be safely discharged from the hospital without specialized interventions)</td>
</tr>
</tbody>
</table>

**Definition of Heart Failure**

<table>
<thead>
<tr>
<th>Classification</th>
<th>Ejection Fraction</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>I. Heart Failure with Reduced Ejection Fraction (HFrEF)</td>
<td>≤40%</td>
<td>Also referred to as systolic HF. Randomized clinical trials have mainly enrolled patients with HFrEF and it is only in these patients that efficacious therapies have been demonstrated to date.</td>
</tr>
<tr>
<td>II. Heart Failure with Preserved Ejection Fraction (HFpEF)</td>
<td>≥50%</td>
<td>Also referred to as diastolic HF. Several different criteria have been used to further define HFpEF. The diagnosis of HFpEF is challenging because it is largely one of excluding other potential noncardiac causes of symptoms suggestive of HF. To date, efficacious therapies have not been identified.</td>
</tr>
<tr>
<td>a. HFpEF, Borderline</td>
<td>41% to 49%</td>
<td>These patients fall into a borderline or intermediate group. Their characteristics, treatment patterns, and outcomes appear similar to those of patients with HFrEF.</td>
</tr>
<tr>
<td>b. HFpEF, Improved</td>
<td>&gt;40%</td>
<td>It has been recognized that a subset of patients with HFpEF previously had HFrEF. These patients with improvement or recovery in EF may be clinically distinct from those with persistently preserved or reduced EF. Further research is needed to better characterize these patients.</td>
</tr>
</tbody>
</table>

**Natural History of Heart Failure**

- **Survival:** 100%
- **Annual Mortality:**
  - Asymptomatic: 0%
  - Mild: 10%
  - Moderate: 20 - 30%
  - Severe: 30 - 40%

**Heart Failure Pathophysiology**

- **Mechanism of Death:**
  - Sudden Death: 40%
  - Worsened HF: 40%
  - Other: 20%

- **Heart Failure Symptoms:**
  - ANP
  - BNP
- **Activation of RAAS, SNS, ET, and others**
- **Peripheral vasoconstriction**
- **Hemodynamic alterations**
- **Remodeling and progressive worsening of LV function**
- **Morbidity and mortality**

Pathophysiologic Effects of Angiotensin II and Epinephrine/Norepinephrine

- Cardiac Myocyte
  - Hypertrophy
  - Apoptosis
  - Cell Sliding
  - Increased Wall Stress
  - Increased O2 Consumption
  - Impaired Relaxation

- Fibroblast
  - Hyperplasia
  - Collagen Synthesis
  - Fibrosis

- Peripheral Artery
  - Vasoconstriction
  - Endothelial Dysfunction
  - Hypertrophy
  - Decreased Compliance

- Coronary Artery
  - Vasoconstriction
  - Endothelial Dysfunction
  - Atherosclerosis
  - Restenosis
  - Thrombosis

ACC/AHA HF Guidelines 2013: Management of HFrEF (Stage C)

Life Prolonging Medical Therapy

- ACE inhibitors or ARB (Class I, evidence A) all patients without contraindications or intolerance
- β-Blockers (Class I, evidence A) all patients without contraindications or intolerance
- Aldosterone antagonists (Class I, evidence A) all patients with Class II-IV HF without contraindications or intolerance, when close monitoring can be assured

Effect of ACE Inhibitors on Mortality and Hospitalizations in Patients with HF

- 32 Trials of ACEI in Heart Failure
- ACEI (n = 3870) Placebo (n = 3235)
- Collaborative Group on ACE Inhibitor Trials

- ATLAS: 8% reduction in death and 14% reduction in death and HF hospitalization
- SOLVD: 14% reduction in death and 26% reduction in death and HF hospitalization

High vs Low Dose ACEI Therapy for Heart Failure

<table>
<thead>
<tr>
<th></th>
<th>Low Dose</th>
<th>High Dose</th>
<th>OR</th>
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<tbody>
<tr>
<td>Death or Hospitalization</td>
<td>1339/1596</td>
<td>1251/1568</td>
<td>0.88</td>
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<tr>
<td>Death</td>
<td>717/1596</td>
<td>666/1568</td>
<td>0.92</td>
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</tbody>
</table>

OR 0.77 (0.67-0.88) p<0.001

**CHARM-Alternative**

Primary outcome of CV death or CHF hospitalization

![Graph showing proportion with CV death or CHF hospitalization over years for Placebo and Candesartan.]

- **Placebo**
  - 406 (40.0%)
- **Candesartan**
  - 334 (33.0%)

HR 0.77 (95% CI 0.67-0.89), \( P = .0004 \)

Adjusted HR 0.70, \( P < .0001 \)

Number at risk

<table>
<thead>
<tr>
<th></th>
<th>Placebo</th>
<th>Candesartan</th>
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</thead>
<tbody>
<tr>
<td>Years</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td>2</td>
<td>2</td>
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<td></td>
<td>3</td>
<td>3</td>
</tr>
<tr>
<td></td>
<td>4</td>
<td>3.5</td>
</tr>
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</table>

**ACEI/ARB in Heart Failure**

- Indicated for all patients with asymptomatic LV dysfunction and for Class I to IV heart failure.
- Contraindications: hyperkalemia, angioedema, pregnancy
- Titrate to target doses (example: enalapril 10 mg bid, lisinopril 20 qd, ramipril 10 mg qd, benazepril 40 qd, valsartan 160 mg bid, candesartan 32 mg qd)
- Monitor serum potassium and renal function. Advise checking chemistry panel 1-2 weeks after first dose.
- Use of ACE inhibitor together with ARB reserved as a consideration only in patients not candidates for aldosterone antagonist.

**Effects of Aldosterone**

- Cardiac Myocyte: Hypertrophy, Norepinephrine Release
- Fibroblast: Hyperplasia, Collagen Synthesis, Fibrosis
- Peripheral Artery: Vasocostriction, Endothelial Dysfunction, Hypertrophy, Decreased Compliance
- Kidney: Potassium Loss, Sodium Retention

**RALES: Aldosterone Antagonist Reduces All-Cause Mortality in Chronic HF**

![Graph showing probability of survival over months for Spironolactone (25 mg) + standard care and Placebo + standard care.]

- HR = 0.70 (95% CI, 0.60 to 0.82)
- \( P < .001 \)

HR = hazard ratio; RR = risk reduction.

*Ejection fraction \( \leq 35\% \) Class III or IV symptoms at some point in prior 2 months.
**Eplerenone in Patients with Systolic Heart Failure and Mild Symptoms: EMPHASIS HF**

**Primary Endpoint: CV Mortality and HF Hospitalization**

HR = 0.63 (0.54-0.74), \( p < 0.001 \)

<table>
<thead>
<tr>
<th>Years from Randomization</th>
<th>Placebo</th>
<th>Eplerenone</th>
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<tr>
<td>0</td>
<td>1373</td>
<td>1364</td>
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<tr>
<td>1</td>
<td>848</td>
<td>925</td>
</tr>
<tr>
<td>2</td>
<td>512</td>
<td>562</td>
</tr>
<tr>
<td>3</td>
<td>199</td>
<td>232</td>
</tr>
</tbody>
</table>


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**Aldosterone Antagonists in Heart Failure**

- Indicated for patients with mild, moderate, or severe HF due to LVD (LVEF ≤ 0.40). (Contraindications: hyperkalemia, Cr > 2.5 in men and > 2.0 in women)

- Spironolactone 12.5 mg PO qd starting dose (or 6.25 mg in higher risk patients) or Eplerenone 25 mg qd (or 12.5 mg in higher risk patients). Decrease potassium supplementation and loop diuretic dose at time of initiation.

- Critical to very closely monitor serum potassium and renal function. Advise checking chemistry panel at 72 hours, 1 week, and 4 weeks.

- Advance Spironolactone dose at 4 weeks to 25 mg PO qd or Eplerenone 50 mg which is the target dose. Avoid higher doses due to risk of hyperkalemia.

**The Use of Beta Adrenergic Blocking Agents in Heart Failure**

Initial hemodynamic deterioration followed by reverse remodeling (decrease in EDV and ESV) with improved ventricular function over time (increased LVEF)

- US Heart Failure Trials Program
- 1094 Class II-IV CHF pts on triple therapy (ACEI, digoxin, diuretics)
- Carvedilol 6.25 bid test 2 weeks, then 12.5 bid, then 25 bid vs placebo

**Effect of Carvedilol in Heart Failure**

- P=0.01

### Major Trials of β-Blockade in Heart Failure

<table>
<thead>
<tr>
<th>Trial</th>
<th>Patients (n)</th>
<th>Follow-up (yrs)</th>
<th>NYHA Class</th>
<th>LVEF (%)</th>
<th>Effects on Outcomes</th>
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<tbody>
<tr>
<td>CIBIS</td>
<td>641</td>
<td>1.9</td>
<td>II-III</td>
<td>≤ 35</td>
<td>All-cause mortality: ↓ 22% NS</td>
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<tr>
<td>CIBIS-II</td>
<td>2647</td>
<td>1.3</td>
<td>II-III</td>
<td>≤ 35</td>
<td>All-cause mortality: ↓ 34% (P&lt;.0001)</td>
</tr>
<tr>
<td>MDC</td>
<td>393</td>
<td>1</td>
<td>II-III</td>
<td>≤ 40</td>
<td>Death or need for transplant: ↓ 30%, (P&lt;.05)</td>
</tr>
<tr>
<td>MERIT-HF</td>
<td>3991</td>
<td>1</td>
<td>II-III</td>
<td>≤ 40</td>
<td>All-cause mortality: ↓ 34% (P&lt;.0002)</td>
</tr>
<tr>
<td>US Carvedilol</td>
<td>1094</td>
<td>7.5 months</td>
<td>II-III</td>
<td>≤ 35</td>
<td>All-cause mortality: ↓ 65% (P&lt;.0001)</td>
</tr>
<tr>
<td>COPERNICUS</td>
<td>2289</td>
<td>10.5 months</td>
<td>IV</td>
<td>≤ 25</td>
<td></td>
</tr>
</tbody>
</table>

### Early Benefits and Early Safety of Carvedilol in Severe HF: COPERNICUS

**Early Mortality Reduction**

- **Placebo**: \(n=1,133\) 2.3%; 30-day risk: 5.1%
- **Carvedilol**: \(n=1,156\) 1.7%; 30-day risk: 5.1%

**Risk Reduction**: ↓ 25% \((-35\% \text{ to } -59\%)\)

**Lower Risk for Worsening CHF**

- **All Patients**: \(n=1,133\) 6.4% 31-day risk: 5.1%
- **Highest-Risk Subgroup**: \(n=1,156\) 11.4% 31-day risk: 8.8%

### Effect of Carvedilol in Severe Heart Failure COPERNICUS

- 2289 Class IV CHF pts, LVEF ≤ 0.25, not on inotropes x 3 days
- Average age 63; LVEF 0.20
- Carvedilol 1.25 mg bid, x 2 weeks titration; 75% to target, withdrew 18% placebo, 15% carvedilol
- Packer, NEJM 2001;344:1651–8

### Effect of Carvedilol Dose on Mortality in Patients with Heart Failure

**Carvedilol Dose-Response Trial (MOCHA)**

- **Placebo**: 6.25 mg bid 5.6%; 0.05
- **Carvedilol**: 12.5 mg bid 6.1%; \(p<0.001\)
- **Carvedilol**: 25 mg bid 11.1%; \(p<0.001\)

**Dose Response of Carvedilol in moderate heart failure patients on all cause mortality**

- Bristow, Circulation 1996;94:1807
**Effects of Sympathetic Activation in Heart Failure**

- **β1-** receptors
- **β2-** receptors
- α1- receptors
- Activation of RAS
- CNS sympathetic outflow
- Cardiac sympathetic activity
- Sympathetic activity to kidneys + blood vessels
- Myocyte death
- Increased arrhythmias
- Vasoconstriction
- Sodium retention
- Disease progression

**Not All β-Blockers Reduce Mortality in HF**

- **BEST** Risk Reduction ↓ 10% (2%, 22%)
- **SENIORS** Risk Reduction ↓ 12% (-8%, 29%)

**β-Blockers Differ in Their Long-Term Effects on Mortality in HF**

- Bisoprolol
  - Beneficial
- Bucindolol
  - No effect
- Carvedilol
  - Beneficial
  - Not well studied
- Metoprolol tartrate
  - Beneficial
  - Not well studied
- Metoprolol succinate
  - Beneficial
- Nebivolol
  - No effect
- Xamoterol
  - Harmful

**COMET: Effect Carvedilol vs Metoprolol Tartrate on Mortality in HF**

- Metoprolol Tartrate
- Carvedilol
- Extrapolation from the survival curves suggested that carvedilol extended median survival by 3.8 years as compared with metoprolol tartrate.

- Metoprolol tartrate mean dose: 85 mg QD; Carvedilol mean dose: 42 mg QD.

**COMET did not evaluate metoprolol succinate, the agent used in the MERIT-HF Trial**

**Beta Blocker Therapy in Heart Failure**

- Indicated for all patients with asymptomatic LVD dysfunction and for Class I to IV Heart Failure with LVEF ≤ 0.40
- Contraindications: cardiogenic shock, severe reactive airway disease, 2/3rd degree HB
- Use one of the 3 evidence-based beta blockers in HF: eg carvedilol, metoprolol succinate, bisoprolol
- Start at very low HF doses and up-titrade to target doses at two week intervals, or highest dose short of target dose that is well tolerated
- Monitor HR and BP


**Neurohormonal Activation as the Therapeutic Target in Heart Failure**

*Therapies with Demonstrated Benefit in Clinical Trials*

- Sympathetic Nervous System
  - Beta Adrenergic Blockers
- Renin Angiotensin Aldosterone System
  - Angiotensin Converting Enzyme Inhibitors
  - (Angiotensin II Receptor Antagonists)
  - Aldosterone Antagonists

**Nepriyisn Inhibition Potentiates Actions of Endogenous Vasoactive Peptides That Counter Maladaptive Mechanisms in Heart Failure**

- **Endogenous vasoactive peptides**
  - (natriuretic peptides, adrenomedullin, bradykinin, substance P, calcitonin gene-related peptide)
- SNS, RAAS activation
- Vascular tone
- Cardiac fibrosis, remodeling
- Sodium retention
- Neprilysin
- Inactive metabolites


**Nepriyisn Levels in Blood Predict Outcomes in HF Patients**

- NEP < median
- NEP ≥ median

Bayés-Genís A et al. JACC. 82: 487-490, 2014
**PARADIGM-HF Trial: Design**

**Entry Criteria:**
- NYHA Class II-IV HF, LVEF ≤40% → amended to ≤35%
- BNP ≥150 pg/mL (or NT-proBNP ≥ 600 pg/mL) or 1/3 lower if hospitalized for HF within 12 mos
- On a stable dose of ACEI or ARB equivalent to ≥10 mg of enalapril daily for ≥4 weeks
- Unless contraindicated, on stable dose of beta-blocker for ≥4 weeks
- SBP ≥95 mm Hg, eGFR ≥30 mL/min/1.73 m² and serum K ≤5.4 mmol/L at randomization

**Specifically designed to test replacing current use of ACEI and ARB as the cornerstone of the treatment of HF**

**PARADIGM-HF: Cardiovascular Death or Heart Failure Hospitalization (Primary Endpoint)**

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

**Days After Randomization**

<table>
<thead>
<tr>
<th>Patients at Risk</th>
<th>Sac/Val (n=4187)</th>
<th>Enalapril (n=4212)</th>
<th>HR</th>
<th>95% CI</th>
<th>p-Value for Interaction</th>
</tr>
</thead>
<tbody>
<tr>
<td>Days after Randomization</td>
<td>2 Week</td>
<td>4–6 Week</td>
<td>2 Weeks</td>
<td>4–6 Week</td>
<td>2 Weeks</td>
</tr>
<tr>
<td>0</td>
<td>3663</td>
<td>3883</td>
<td>0.58</td>
<td>0.50–0.70</td>
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</tr>
<tr>
<td>120</td>
<td>4895</td>
<td>5212</td>
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<td>0.39–0.59</td>
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</tr>
<tr>
<td>240</td>
<td>5722</td>
<td>6048</td>
<td>0.45</td>
<td>0.37–0.54</td>
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<tr>
<td>360</td>
<td>6559</td>
<td>6902</td>
<td>0.43</td>
<td>0.35–0.53</td>
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<tr>
<td>480</td>
<td>7397</td>
<td>7762</td>
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<td>0.33–0.51</td>
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<tr>
<td>600</td>
<td>8245</td>
<td>8645</td>
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<td>0.31–0.50</td>
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</tr>
<tr>
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<td>9093</td>
<td>9517</td>
<td>0.38</td>
<td>0.30–0.49</td>
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<tr>
<td>840</td>
<td>9941</td>
<td>10383</td>
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<td>0.28–0.47</td>
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<tr>
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<td>10789</td>
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<td>0.05–0.26</td>
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</tr>
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<td>0.04–0.25</td>
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<td>0.03–0.24</td>
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<td>3960</td>
<td>31989</td>
<td>32653</td>
<td>0.10</td>
<td>0.02–0.23</td>
<td>0.0000001</td>
</tr>
<tr>
<td>4080</td>
<td>32837</td>
<td>33501</td>
<td>0.09</td>
<td>0.01–0.22</td>
<td>0.0000001</td>
</tr>
<tr>
<td>4200</td>
<td>33685</td>
<td>34349</td>
<td>0.08</td>
<td>0.00–0.21</td>
<td>0.0000001</td>
</tr>
</tbody>
</table>

**Sac/Val Better**

**HR = 0.80 (0.73–0.87)**

**P = 0.0000002**

**Number needed to treat = 21**
# PARADIGM-HF: Adverse Events

<table>
<thead>
<tr>
<th>Prospectively identified adverse events</th>
<th>Sac/Val (n=4187)</th>
<th>Enalapril (n=4212)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Symptomatic hypotension</td>
<td>14.0%</td>
<td>9.2%</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Serum potassium ≥ 6.0 mmol/L</td>
<td>4.3%</td>
<td>5.6%</td>
<td>0.007</td>
</tr>
<tr>
<td>Serum creatinine ≥ 2.5 mg/dL</td>
<td>3.3%</td>
<td>4.5%</td>
<td>0.007</td>
</tr>
<tr>
<td>Cough</td>
<td>11.3%</td>
<td>14.3%</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Discontinuation for adverse event</td>
<td>16.7%</td>
<td>12.3%</td>
<td>0.03</td>
</tr>
<tr>
<td>Discontinuation for hypotension</td>
<td>0.9%</td>
<td>0.7%</td>
<td>0.38</td>
</tr>
<tr>
<td>Discontinuation for hyperkalemia</td>
<td>0.3%</td>
<td>0.4%</td>
<td>0.56</td>
</tr>
<tr>
<td>Discontinuation for renal impairment</td>
<td>0.7%</td>
<td>1.4%</td>
<td>0.002</td>
</tr>
<tr>
<td>Angioedema (adjudicated)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Medications, no hospitalization</td>
<td>6 (0.1%)</td>
<td>4 (0.1%)</td>
<td>0.52</td>
</tr>
<tr>
<td>Hospitalized; no 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>


# FDA-Approved Sacubitril/Valsartan

<table>
<thead>
<tr>
<th>Brand name</th>
<th>Entresto</th>
</tr>
</thead>
<tbody>
<tr>
<td>Indication</td>
<td>The fixed-dose combination of the neprilysin inhibitor sacubitril and the ARB valsartan is indicated to reduce the risk of CV death and HF hospitalization in patients with HF with reduced ejection fraction.</td>
</tr>
<tr>
<td>Dosage</td>
<td>Start with 48/51 mg twice daily. Double the dose after 2–4 weeks as tolerated to maintenance dose of 97/103 mg twice daily.</td>
</tr>
<tr>
<td>Renal/hepatic impairment</td>
<td>For patients not currently taking an ACEi or ARB, or for those with severe renal impairment (eGFR &lt;30 mL/min/1.73 m²) or moderate hepatic impairment, start with 24/26 mg twice daily.</td>
</tr>
<tr>
<td>Switching from an ACE inhibitor</td>
<td>Stop ACE inhibitor for 36 hours before starting treatment.</td>
</tr>
<tr>
<td>Contraindications</td>
<td>History of angioedema related to previous ACE inhibitor or ARB, concomitant use of ACE inhibitors, concomitant use of aldosterone antagonists, or diabetes. WARNING – pregnancy, hyperkalemia.</td>
</tr>
<tr>
<td>Side effects</td>
<td>Hypotension, hyperkalemia, cough, dizziness, renal failure, and angioedema (0.5% Sac/Val vs. 0.2% Enalapril).</td>
</tr>
</tbody>
</table>


# 2016 ACC/AHA/HFSA Heart Failure Guideline Update

**Pharmacological Treatment for Stage C HF/EF**

**Inclusion:**
- Admitted to hospital with primary diagnosis of HF, NYHA class II–IV, including signs and symptoms of fluid overload
- At randomization (between 24 hours and 10 days from initial presentation), hospitalized patients were defined as stable by:
  - SBP ≥100 mmHg for 6 hours prior to randomization, no symptomatic hypotension
  - No increase (intensification) in IV diuretic dose within 6 hours prior to randomization
  - No IV inotropic drugs for 24 hours prior to randomization
  - No IV vasodilators including nitrates within last 6 hours prior to randomization
  - LVEF ≤40%
  - NT-proBNP ≥1600 pg/mL OR BNP ≥400 pg/mL during current hospitalization

**Exclusion:**
- Hypersensitivity, contraindications or intolerance to study drugs
- Known history of angioedema with ACEi/ARB
- eGFR <30ml/min/1.73m²
- Serum potassium >5.2mEq/L at screening
- Primary dyspnea from non-cardiac, non-heart failure cause
- Implantation of cardiac resynchronization device in 3 months prior to randomization
- Pregnancy or potential to become pregnant (not using two birth control methods)

**Primary End Point**
- Time-averaged proportional change in NT-proBNP at weeks 4 and 8

**Exploratory Clinical Outcomes**
- To examine the effect of sacubitril/valsartan on incidence of rehospitalization through day 30


# PIONEER-HF: In-Hospital ARNI

**Inclusion:**
- To Evaluate the In-Hospital Initiation of Sacubitril/Valsartan in Stabilized Patients Hospitalized with HFrEF irrespective of Prior HF Diagnosis or ACEi/ARB use

**Exclusion:**
- Hypersensitivity, contraindications or intolerance to study drugs
- Known history of angioedema with ACEi/ARB
- eGFR <30ml/min/1.73m²
- Serum potassium >5.2mEq/L at screening
- Primary dyspnea from non-cardiac, non-heart failure cause
- Implantation of cardiac resynchronization device in 3 months prior to randomization
- Pregnancy or potential to become pregnant (not using two birth control methods)

Neurohormonal Activation as the Therapeutic Target in Heart Failure

Therapies with Demonstrated Benefit in Clinical Trials

- Sympathetic Nervous System
- Beta Adrenergic Blockers
- Renin Angiotensin Aldosterone System
  - Angiotensin Receptor Neprilysin Inhibitor
  - Aldosterone Antagonists

AHeFT: Trial Summary

1,050 African Americans with Class III to IV HF, LVEF 24%, on ACEI, BB, AA

43% Decrease in Mortality

Fixed-dose HYD/ISDN vs Placebo

- All-Cause Mortality (%)
- First HF Hospitalization (%)
- Patient Reported Functional Status

HYD/ISDN = hydralazine/isosorbide dinitrate
Resting Heart Rate and CV Outcomes in Patients with HF

Resting heart rate is an important predictor of mortality and CV outcomes in patients with HF

<table>
<thead>
<tr>
<th>Tertile 1: Median heart rate 60 bpm</th>
<th>Tertile 2: Median heart rate 72 bpm</th>
<th>Tertile 3: Median heart rate 85 bpm</th>
</tr>
</thead>
<tbody>
<tr>
<td>All-Cause Mortality</td>
<td>CV Death or WHFH</td>
<td></td>
</tr>
<tr>
<td>Probability</td>
<td>Probability</td>
<td></td>
</tr>
</tbody>
</table>

Resting heart rate is an important predictor of mortality and CV outcomes in patients with HF

SHIFT Study: Primary Endpoint of CV Death or Hospitalization for Worsening HF

©2015 patients with LVEF ≤35%. Sinus rhythm ≥70 bpm

Ivabradine

- Specific inhibitor of the I_f current in SA node
- This so-called “funny” current controls the rate of spontaneous activity of SA node myocytes
- Reduces the slope for diastolic depolarization
- Prolongs Diastolic Duration → Slows Heart Rate
- No action on other cardiac channels
- Does not modify cardiac contractility

FDA-Approved Ivabradine

<table>
<thead>
<tr>
<th>Ivabradine</th>
</tr>
</thead>
<tbody>
<tr>
<td>Brand name</td>
</tr>
<tr>
<td>Indication</td>
</tr>
<tr>
<td>Dosage</td>
</tr>
<tr>
<td>Contraindications</td>
</tr>
<tr>
<td>Side effects</td>
</tr>
</tbody>
</table>

**Effect of Digoxin on Mortality in Heart Failure: The Digitalis Investigation Group**

- **CV Mortality**: +6%
- **HF Hospitalizations**: +28%
- **Total Hospitalizations**: +6%

**Mortality from Any Cause (%)**

**Relative Risk 0.99**

95% CI 0.91–1.07

*P*= .80

All-cause mortality rates: Placebo 35.1%; Digoxin 34.8%

All patients were randomized to digoxin (n=3,403) or placebo (n=3,397) in addition to therapy with diuretics and ACEI followed for 37 months.

**Digoxin**

**Placebo**

0 4 8 12 16 20 24 28 32 36 40 44 48 52

0 10 20 30 40 50

**Diuretic Therapy in Chronic Heart Failure**

- **Loop diuretics are mainstay of therapy for HF (Given to > 85% of patients)**

  - Beneficial effects of diuretic therapy:
    - ↓ Dyspnea and other congestive symptoms
    - ↓ Volume overload
    - Facilitate successful initiation and titration of ACE inhibitors, β-blockers, vasodilators

**No outcome studies of diuretic therapy in chronic HF and effects on morbidity and mortality unknown**

**Important Comorbidities in Heart Failure**

- **Cardiovascular**
  - Hypertension
  - Coronary artery disease
  - Peripheral vascular disease
  - Cerebral vascular disease
  - Hyperlipidemia
  - Atrial fibrillation

- **Non-Cardiovascular**
  - Obesity
  - Diabetes
  - Anemia
  - Chronic kidney disease
  - Thyroid disease
  - COPD / Asthma
  - Smoking
  - Sleep disordered breathing
  - Liver disease
  - Arthritis
  - Cancer
  - Depression

**Diabetes and Heart Failure**

- The two diseases entities are highly co-prevalent
- Diabetes contributes to disease progression in HF and is associated with substantially worse prognosis, even when conventional HF therapies are applied
  - Of patients hospitalized with HF, 42-46% have diabetes and these patients are at greater risk of rehospitalizations and mortality
- The choice of pharmacologic glycemic management can markedly impact heart failure outcomes
  - Certain therapies are neutral or associated with harm
  - Certain therapies markedly improve outcomes
- Pharmacologic glycemic management is a critical component of HF management

Diabetes and Heart Failure

Heart Failure Rates in Diabetes Glucose Control Trials

Risk of HF events with glucose-lowering drugs or strategies versus standard care

- PPAR Agonists
- DPP-4 Inhibitors
- Intensive Control
- Insulin
- Weight loss

SGLT2 Inhibitors

- Virtually all glucose filtered by the kidney is reclaimed in the proximal tubule. ¹ Sodium glucose cotransporter 2 (SGLT2) is responsible for 90% of this reabsorption.
- Selective inhibitors of SGLT2 have been developed. ²
- By reducing renal glucose reabsorption, SGLT2 inhibitors increases urinary glucose excretion.³
- In patients with type 2 DM, SGLT2 inhibitors leads to:⁴
  - Significant reductions in HbA1c
  - Weight loss
  - Reductions in BP without increases in heart rate

EMPA-REG OUTCOME Trial

EMPA-REG OUTCOME Trial: Key Results

- Primary Endpoint (3P MACE) ↓ 14% (p=0.0382)
- MI ↓
- Stroke ↓
- CV DEATH ↓ 38% (p<0.0001)
- All-Cause Mortality ↓ 32% (p<0.0001) Driven by CV Death

Heart Failure
- Hospitalization for Heart Failure ↓ 35% (p=0.0017)
- Hospitalization for Heart Failure or CV Death ↓ 34% (p<0.0001)

Patients without heart failure at baseline

- HR 0.63 (95% CI 0.51, 0.78)
- 7.1
- 4.5

Patients with heart failure at baseline

- HR 0.72 (95% CI 0.59, 1.04)
- 20.1
- 16.2

Heart Failure with Preserved Ejection Fraction

Treatment of patients with predominantly diastolic dysfunction heart failure has not been well studied.

Control hypertension

Diuretics should be used cautiously, at low dose initially, recognizing that the stiff heart is highly dependent on adequate preload.

Rate control for atrial fibrillation

ACE inhibitors, calcium channel blockers, and beta blockers have favorable effects upon hemodynamics but their impact on longer term outcome is not known.

Patient Education is Essential in HF

Patient Instructions
- Monitor daily weights
- Salt restricted diet (e.g. 2-3 gm sodium diet)
- Medications, need for adherence
- Activity Rx
- Smoking Cessation Advice/Counseling
- What to do if HF symptoms worsen
- Close follow-up and monitoring

HF Management Is Multidimensional

Destination VAD Therapy Trials

Triggers for Referral to HF Specialist

Evidence-Based HFrEF Therapies

Use and Dosing of GDMT for HFrEF: CHAMP HF Registry
ACC/AHA: Implementation of Guidelines

- Academic detailing or educational outreach visits are useful to facilitate the implementation of practice guidelines
- Chart audit and feedback of results can be effective to facilitate implementation of practice guidelines
- The use of reminder systems can be effective to facilitate implementation of practice guidelines
- The use of performance measures based on practice guidelines may be useful to improve quality of care


2017 ACC Expert Consensus Decision Pathway for Optimization of HF Treatment


Improved Adherence to HF Guidelines Translates to Improved Clinical Outcomes in Real World Patients

Each 10% improvement in guideline recommended composite care was associated with a 13% lower odds of 24-month mortality (adjusted OR 0.87; 95% CI, 0.84 to 0.90; P<0.0001).


TreatHF: an App for Heart Failure

This app helps clinicians confirm which therapies are suggested for their symptomatic heart failure patients with reduced ejection fraction (HREF) and provides guidance on the use of each therapy.

- Enter patient indications
- Review individualized next steps for medical therapy
- Email or print a summary of the next steps
- Reference detailed information on:
  - Initiation, titration, and monitoring of each medication
  - Guidance for optimizing your overall medication strategy

Information in this app is derived from the 2017 ACC Expert Consensus Decision Pathway for Optimization of Heart Failure Treatment, the 2017 ACC/AHA/HFSA Focus Update of the 2013 ACCF/AHA Guideline for the Management of Heart Failure, and the 2013 ACCF/AHA Guideline for the Management of Heart Failure. Indications collected in the app reflect the evidence-based indications outlined in these documents, and are meant to serve as a starting point to support clinical decisions. TreatHF is available on the web, or to download for phones and tablets.
Potential Impact of Optimal Implementation of Evidence-Based HFrEF Therapies on Mortality

<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>(6616-22,229)</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>(53,013-158,814)</td>
</tr>
</tbody>
</table>


Cumulative Impact of Clinical Trial Evidence Based Heart Failure Therapies

<table>
<thead>
<tr>
<th>Relative-risk</th>
<th>2 yr Mortality</th>
</tr>
</thead>
<tbody>
<tr>
<td>None</td>
<td>- -</td>
</tr>
<tr>
<td>ACEI or ARB</td>
<td>23%</td>
</tr>
<tr>
<td>Beta Blocker</td>
<td>35%</td>
</tr>
<tr>
<td>Aldosterone Ant</td>
<td>30%</td>
</tr>
<tr>
<td>CRT-D (EF&lt;35, QRS&gt;120)</td>
<td>36%</td>
</tr>
<tr>
<td>ARNI</td>
<td>16%</td>
</tr>
</tbody>
</table>

Cumulative risk reduction if all evidence-based therapies are used: 80%
Absolute risk reduction: 28.1%, NNT = 3.6


Heart Failure Prevention

Patients at risk for heart failure:
- Treat systolic and diastolic hypertension according to guidelines
- Treat diabetes according to guidelines
- Treat atherosclerosis according to guidelines
- Treat lipid disorders according to guidelines
- Encourage smoking cessation
- Encourage exercise
- Discourage heavy alcohol intake, illicit drug use
- Consider ACEI/ARB and beta blocker use in those at risk for HF


Advances in the Treatment of HF

- Increased attention to prevention
- ACEI / β-blocker / aldosterone antagonist combination previously established “cornerstone” of therapy
- ARNI further reduce morbidity and mortality, replace ACEI/ARB
- Evidence that β-blockers’ effects are not homogeneous
- Downgrade in recommendation for use of digoxin
- Integration of CRT and ICD device therapy into the standard therapeutic regimen
- Recognition that “special populations” of HF patients may benefit from or require different approaches
- New strategies to improve utilization of evidence based therapies

The economic burden of HF continues to grow and HF is one of the single most expensive and deadly health care problems.

Medical therapies and nonpharmacologic measures for HF that can impact patients’ need for re-hospitalization, costs of care, and survival are underutilized in conventional practice settings.

Every effort should be made to implement evidence-based HF therapies when indicated and optimize care of HF.

Every effort should be made to prevent HF.